Check for updates

### **OPEN ACCESS**

EDITED BY Shao Hui Huang, University Health Network, Canada

#### REVIEWED BY Qiaojuan Guo, Fujian Provincial Cancer Hospital, China Marc Oliva, Catalan Institute of Oncology, Spain Sareh Keshavarzi, University Health Network, Canada

\*CORRESPONDENCE Bi-Cheng Wang bcsnowell@163.com

SPECIALTY SECTION This article was submitted to Head and Neck Cancer, a section of the journal Frontiers in Oncology

RECEIVED 24 April 2022 ACCEPTED 05 July 2022 PUBLISHED 29 July 2022

#### CITATION

Wang B-C, Kuang B-H, Liu X-X, Lin G-H and Liu Q (2022) Induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: A systematic review and meta-analysis. *Front. Oncol.* 12:927510. doi: 10.3389/fonc.2022.927510

#### COPYRIGHT

© 2022 Wang, Kuang, Liu, Lin and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in

accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# Induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: A systematic review and meta-analysis

Bi-Cheng Wang<sup>1</sup>\*, Bo-Hua Kuang<sup>1</sup>, Xin-Xiu Liu<sup>1</sup>, Guo-He Lin<sup>2</sup> and Quentin Liu<sup>3</sup>

<sup>1</sup>Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, <sup>2</sup>Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China, <sup>3</sup>State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Cancer Center, Sun Yat-sen University, Guangzhou, China

**Background:** Adding induction chemotherapy to concurrent platinum-based chemoradiotherapy has significantly prolonged the survival time of patients with locoregionally advanced nasopharyngeal carcinoma. In this study, we intend to evaluate the survival outcomes, responses, and incidences of toxicities of induction chemotherapy and the differences between different strategies.

**Methods:** A comprehensive search was conducted in PubMed, Embase, Web of Science, and Cochrane CENTRAL on August 10, 2021. Single-arm or multi-arm prospective clinical trials on induction chemotherapy without targeted therapies or immune checkpoint inhibitors were included. Primary outcomes included survival outcomes, objective response rate, and disease control rate, and the secondary outcome was the rates of grade 3 or higher treatment-related adverse events.

**Results:** The 39 studies included in the systematic review and meta-analysis comprised 36 clinical trials and 5389 patients. The estimates for 3-year overall and fail-free survival rates were 87% and 77%. The estimates for 5-year rates of overall and fail-free survival were 81% and 73%. Gemcitabine plus platinum and docetaxel combined with 5-fluorouracil plus platinum strategies were associated with the highest rates of 3-year and 5-year overall survival. The objective response and disease control rates were 85% and 98% after the completion of induction chemotherapy. Neutropenia (27%) and nausea/ vomiting (7%) were the most common grade 3 or higher treatment-related hematological and non-hematological adverse events during the induction phase.

**Conclusions:** Different induction chemotherapeutic strategies appear to have varying effects and risks; a comprehensive summary of the survival outcomes, responses, and toxicities in clinical trials may provide a crucial guide for clinicians.

### KEYWORDS

induction chemotherapy, nasopharyngeal carcinoma, meta-analysis, concurrent chemoradiotherapy (CCRT), responses, safety

## Introduction

It is estimated that over 70% of nasopharyngeal carcinoma (NPC) patients presented with locoregional advanced stage (1). For this population, platinum-based concurrent chemoradiotherapy (CCRT) is the backbone of the radical treatment (2, 3). For furtherly elevating the responses and prolonging survival outcomes, induction chemotherapy has been administered before CCRT. For instance, the addition of docetaxel, cisplatin, and 5-fluorouracil reduced 32% and 41% of the 3-year risks of disease progression and death (4); Gemcitabine and cisplatin induction chemotherapy significantly decreased the hazard ratio for 3-year recurrence and death by 49% and 57% in locoregionally advanced NPC patients (5). According to the latest guidelines for nasopharyngeal carcinoma, induction chemotherapy followed by CCRT is recommended as the preferred standard of care for patients with locoregionally advanced NPC (6–8).

Although adding induction chemotherapy to CCRT has been demonstrated to be superior to CCRT alone (9), substantial variations exist in different populations, induction chemotherapeutic regimens, cycles, and CCRT strategies. Ignoring these variations might lead to an inaccurate evaluation of the true efficacy and safety profile associated with induction chemotherapy.

For aiding clinical decision-making, we performed a systematic review and meta-analysis to integrate the benefits and risks of induction chemotherapy in published prospective studies and comprehensively describe the potential differences among a variety of populations, induction chemotherapeutic regimens, cycles, and CCRT strategies.

## Methods

## Search methods and study selection

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (10). A comprehensive search of Englishlanguage prospective clinical trials was performed in PubMed, Embase, Web of Science, and Cochrane CENTRAL with the search terms (nasopharyngeal carcinoma) AND (induction chemotherapy OR neoadjuvant chemotherapy) AND (radiotherapy OR chemoradiotherapy) AND (trial OR clinical trial) on August 10, 2021. The references of relevant published clinical studies and review literatures were also searched for additional eligible trials. Inclusion criteria included: (1) Participants: over 18 years old locoregionally advanced NPC patients; (2) Interventions: induction chemotherapy followed by platinum-based CCRT; (3) Outcomes: data on survival outcomes, responses, and treatment-related adverse events were available. Single-arm and multi-arm studies were eligible. However, patients who received subsequent adjuvant chemotherapy, targeted therapy, or immunotherapy were excluded. Two authors performed the literature search and study selection independently, and any discrepancies were reviewed by a third author and resolved by consensus.

### Outcome measures and data extraction

The primary outcome measures comprised the 3- and 5-year survival rates, objective response rate (ORR, defined as the percentage of patients with a response of complete response and partial response), and disease control rate (DCR, defined as the percentage of patients with a response of complete response, partial response, and stable disease) after induction chemotherapy, at the end of CCRT, and at 3 months post CCRT. The secondary outcome was the incidence of grade 3 or higher treatment-related adverse events during induction chemotherapy and CCRT phases. Overall survival (OS) was defined as the time from diagnosis or random assignment to death because of any cause; failure-free survival (FFS) was defined as the time from diagnosis or random assignment to documented disease recurrence; locoregional recurrence-free survival (LRFS) was defined as the time from diagnosis or random assignment to locoregional disease recurrence; distant metastasis-free survival (DMFS) was defined as the time from diagnosis or random assignment to distant metastasis.

Data extraction was conducted by two authors independently and reviewed by a third author. Data regarding the number of patients, study design, region, regimens, dosing schedule, survival rates, responses, and the number of grade 3 or more adverse events were recorded.

## Statistical analysis

The response variable is the number of reported survivals, responses, and grade 3 or higher toxic effects, assumed to follow a binomial distribution. Statistical analyses were performed using R Studio (version 1.4.1717, R Foundation for Statistical Computing). The "meta" package was used to perform the random effects metaanalyses, sensitivity analyses, and tests for heterogeneity ( $I^2$  and  $\tau$ ) (11). A random-effects model was selected over a fixed-effects model if  $I^2 > 50\%$  because using random effects is often the preferred technique when conducting a single-arm meta-analysis to guide treatment decisions (12).  $\tau^2 = 0$  meant that no deviations were found across the studies. Otherwise, deviations existed but did not indicate significant heterogeneity. Pooled proportions were estimated via the metaprop function in the "meta" package, applying a logit transformation and continuity correction of 0.5 and other default settings. The Jadad scoring scale was used to assess the quality of each eligible trial (low quality: a score of  $\leq 2$ ; high quality: a score of  $\geq$  3) (13). Publication bias was evaluated by funnel plots, Egger's regression tests, and Begg's test.

## Results

### Eligible studies and characteristics

Literature search and review of reference lists identified 1434 relevant records. After screening and eligibility assessment, we included in the meta-analysis a total of 36 prospective clinical trials involving 5389 patients (Supplement 1). The trials were published between 2004 and 2021, as displayed in Table 1 (14-52). Patients in 26 trials underwent treatment in China, and patients in the other 10 trials underwent treatments in Italy, Korea, Greece, Australia, Austria, Singapore (Ethnic group: 95.3% of enrolled patients were Chinese), Switzerland, India, and Arabia. Induction chemotherapeutic regimens included (1) taxane plus platinum (TP), (2) platinum plus 5-fluorouracil (PF), (3) taxane plus platinum and 5-fluorouracil (TPF), (4) gemcitabine plus platinum (GP), (5) taxane plus platinum and epirubicin, (6) platinum plus epirubicin, (7) platinum plus capecitabine, (8) gemcitabine plus platinum and taxane, (9) mitomycin C plus epirubicin, platinum, and 5-fluorouracil, and (10) taxane plus ifosfamide and platinum. Two or three cycles of induction chemotherapy were administered. Concurrent chemoradiotherapies comprised weekly and triweekly platinum-based strategies. In addition, T3-4N0 and

Supplement 2 shows the quality evaluation for each eligible study, corresponding funnel plots, Egger's tests (P > 0.1), Begg's test (P > 0.1), and sensitivity analyses, indicating a moderate-to-high quality for clinical trials enrolled (16 trials were identified as low quality [a score of  $\leq$  2], while 20 trials as high quality [a score of  $\geq$  3]) and the sole publication bias in the analysis of 5-year OS (Begg's test: P = 0.09).

## Survival rates

The 3-year OS rate was 87% (95% CI, 84%-90%;  $I^2 = 87\%$ ; P < 0.01 for heterogeneity) in 3212 patients across 24 trials, the 3-year FFS rate was 77% (95% CI, 74%-80%;  $I^2 = 68\%$ ; P < 0.01) in 3104 patients across 24 trials, the 3-year LRFS rate was 91% (95% CI, 87%-94%;  $I^2 = 85\%$ ; P < 0.01) in 2245 patients across 15 trials, and the 3-year DMFS rate was 85% (95% CI, 81%-89%;  $I^2 = 86\%$ ; P < 0.01) in 2259 patients across 15 trials (Figure 1).

The 5-year OS rate was 81% (95% CI, 76%-85%;  $I^2 = 83\%$ ; P < 0.01) in 2009 patients across 9 trials, the 5-year FFS rate was 73% (95% CI, 69%-77%;  $I^2 = 73\%$ ; P < 0.01) in 1965 patients across 9 trials, the 5-year LRFS rate was 87% (95% CI, 85%-90%;  $I^2 = 54\%$ ; P = 0.03) in 1595 patients across 7 trials, and the 5-year DMFS rate was 83% (95% CI, 78%-88%;  $I^2 = 85\%$ ; P < 0.01) in 1595 patients across 7 trials (Figure 2).

## **Response rates**

Figure 3 depicts the forest plots for ORR. The estimated ORRs post induction chemotherapy, post CCRT, and post CCRT at 3 months were 85% (95% CI, 80%-90%;  $I^2 = 91\%$ ; P < 0.01), 97% (95% CI, 94%-100%;  $I^2 = 80\%$ ; P < 0.01), and 98% (95% CI, 96%-99%;  $I^2 = 81\%$ ; P < 0.01), respectively.

Figure 4 depicts the forest plots for DCR. The estimated DCRs post induction chemotherapy, post CCRT, and post CCRT at 3 months were 98% (95% CI, 97%-100%;  $I^2 = 66\%$ ; P < 0.01), 98% (95% CI, 93%-100%;  $I^2 = 71\%$ ; P < 0.01), and 96% (95% CI, 87%-100%;  $I^2 = 83\%$ ; P < 0.01), respectively.

# Subgroup analysis of survival outcomes and responses

Figure 5A displays the subgroup analyses regarding population, induction chemotherapeutic regimens, induction chemotherapy cycles, and platinum-based CCRT strategies.

Patients in China achieved higher 3-year FFS (79% [95% CI, 77%-82%] vs. 69% [95% CI, 67%-75]) and LRFS (93% [92%-95%] vs. 82% [95% CI, 67%-93%]) rates, and ORRs (post CCRT: 99% [95% CI, 97%-100%] vs. 89% [95% CI, 82%-95%]; 3-month

### TABLE 1 Characteristics of Patients and Studies.

Author	Year	Phase	Register number	Stage	No. P	Median age (range)	Male (%)	Regimens	Doses	Cycles (%)	CC	RT
Chan	2004	II	_	III-IV 5th AJCC	31	46 (31-55)	77.4	Paclitaxel Carboplatin	70 mg/m2/day, d1+8+15 AUC=6/day, d1	2 (100)	Cisplatin (40 mg/m2/wk)	2DRT
Ferrari	2008	II	-	IIb–IVb 5th AJCC	34	53 (31-57)	67.6	Cisplatin 5-Fluorouracil	100 mg/m2/day, d1 1,000 mg/m2/day, d1–4	3 (100)	Cisplatin (100 mg/m2/3wks)	3DRT
Bae	2009	Π	-	III-IVb AJCC	33	Mean (SD) 50.8 (13.7)	69.7	Docetaxel Cisplatin 5-Fluorouracil	70 mg/m2/day, d1 75 mg/m2/day, d1 1,000 mg/m2/day, d1-4	3 (97.0)	Cisplatin (100 mg/m2/3wks)	-
Huang	2009	-	-	III-IV 92 Chinese stage	201	Mean (SD) 42.7 (10)	77.6	Carboplatin 5-Fluorouracil	AUC=6/day, d1 750 mg/m2/day, d1-5	2 (97.0)	Carboplatin (AUC = 6/3wks)	2DRT
Hui	2009	Π	-	III-IVb 1997 UICC	34	50 (31-70)	61.8	Docetaxel Cisplatin	75 mg/m2/day, d1 75 mg/m2/day, d1	2 (100)	Cisplatin (40 mg/m2/wk)	IMRT
Kong*	2010	Π	-	III-IVb 6th AJCC	59	44 (21-69)	NA	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 500 mg/m2/day, d1-5	3	Cisplatin (40 mg/m2/wk)	3DRT IMRT
Zheng	2010	II	-	IIb-IVb 5th AJCC	60	48 (21-68)	71.7	Nedaplatin 5-Fluorouracil	100 mg/m2/day, d1 700 mg/m2/day, d1-4	3 (10)	Nedaplatin (100 mg/m2/3wks)	IMRT
Fountzilas	2012	Π	ACTRN12609000730202	IIb-IVB 6th AJCC	72	49 (19-82)	70.8	Epirubicin Paclitaxel Cisplatin	75 mg/m2/day, d1 175 mg/m2/day, d1 75 mg/m2/day, d2	3 (86)	Cisplatin (40 mg/m2/wk)	-
Huang	2012/ 2015	-	-	III-IV 92 Chinese stage	201	Mean (SD) 42.7 (10)	77.6	5-Fluorouracil Carboplatin	750 mg/m2/day, d1-5 AUC=6, d1	2 (99.5)	Carboplatin (AUC = 6/3wks)	2DRT
Kong*	2013	Π	NCT00816855 NCT00816816	III–IVb 6th AJCC	116	-	81	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 500 mg/m2/day, d1-5	3	Cisplatin (40 mg/m2/wk)	3DRT IMRT
Lim	2013	II	-	IIb to IV 7th AJCC	28	47.4 (23-71)	67.9	Carboplatin Gemcitabine	AUC=5/day, d1 1 g/m2/day, d1, 8	3 (92.9)	Cisplatin (20 mg/m2/d1-5/3wks)	3DRT IMRT
Zhong	2013	II	-	III–IVb 6th AJCC	46	46 (22-67)	60.9	Docetaxel Cisplatin	75 mg/m2/day, d1 75 mg/m2/day, d1	2 (97.8)	Cisplatin (75 mg/m2/3wks)	-
Rosenblatt	2014	III	-	III–IV 5th UICC	139	Mean (SD) 43.5 (13.6)	74.8	Cisplatin Doxorubicin or Epirubicin or 5-Fluorouracil	100 mg/m2/day, d1 50 mg/m2/day, d1 or 75 mg/m2/day, d1 or -	2	Cisplatin (30 mg/m2/wk)	-
Lee	2015/ 2020	III	NCT00379262	III–IVb 6th AJCC	161	Mean (SD) 48 (9)	72	Cisplatin 5-Fluorouracil	100 mg/m2/day 1000 mg/m2//day, 120h	3	Cisplatin (100 mg/m2/3wks)	2DRT 3DRT
					165	Mean (SD) 48 (9)	80.6	Cisplatin Capecitabine	100 mg/m2/day 2000 mg/m2/14 days	3		IMRT
Tan	2015	II-III	CDR0000657121	III–IVb 97 UICC	86	48.5 (IQR 41.9-54.7)	82.6	Gemcitabine Carboplatin Paclitaxel	1000 mg/m2/day, d1+8 AUC = 2.5/day, d1+8 70 mg/m2/day, d1+8	3	Cisplatin (40 mg/m2/wk)	2DRT IMRT

(Continued)

Autho
Lv
Sun Li
Tang

Author	Year	Phase	Register number	Stage	No. P	Median age (range)	Male (%)	Regimens	Doses	Cycles (%)	CC	RT
Lv	2016	II	-	III–IVb 02 UICC	44	Mean (SD) 45.3 (8.4)	77.3	Docetaxel Carboplatin	70 mg/m2/day AUC=5	2 (100)	Carboplatin (AUC = 5/3wks)	-
					44	Mean (SD) 44.6 (8.9)	75	5-Fluorouracil Carboplatin	800 mg/m2/day, 4 days AUC = 5	2 (97.7)		
Sun Li	2016 2019	III	NCT01245959	III–IVb (except T3-4N0) 7th AJCC	241	42 (IQR 36-49)	80.1	Docetaxel Cisplatin 5-Fluorouracil	60 mg/m2/day, d1 60 mg/m2/day, d1 600 mg/m2/day, d1-5	3 (88)	Cisplatin (100 mg/m2/3wks)	IMRT
Tang	2016	II	NCT01479504	III-IVb 6th AJCC	113	45.05 (28-65)	78.8	Docetaxel Nedaplatin	65 mg/m2/day, d1 80 mg/m2/day, d1	2 (100)	Nedaplatin (40 mg/m2/wk)	IMRT
					110	45.32 (23-65)	77.3	Docetaxel Cisplatin	65 mg/m2/day, d1 80 mg/m2/day, d1	2 (100)	Cisplatin (40 mg/m2/wk)	
Cao Yang	2017 2019	III	NCT00705627 RDDA 2017000111	III-IVb (except T3N0-1) 6th AJCC	238	44 (19-65)	72.7	Cisplatin 5-Fluorouracil	80 mg/m2/day, d1 800 mg/m2/day, d1-5	2 (96.3)	Cisplatin (80 mg/m2/3wks)	2DRT IMRT
Ke-1	2017	II	ChiCTR-ONC-12002615	III-IVb (T3-4N0-3M0 or T1-2N2-3M0) 7th AJCC	36	48 (23-67)	77.8	Nab-paclitaxel Cisplatin	260 mg/m2/day, d1 80 mg/m2/day, d1	2 or 3	Cisplatin (80 mg/m2/3wks)	IMRT
Ke-2	2017	II	ChiCTR-ONC-12002060	III–IVb 7th AJCC	59	43 (19-59)	72.9	Lobaplatin 5-Fluorouracil	30 mg/m2/day, d1 800 mg/m2/day, d1-5	2	Lobaplatin (50 mg/m2/3wks)	IMRT
Kong*	2017	II	-	III–IVb 7th AJCC	116	-	81	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 500 mg/m2/day, d1-5 every 4 weeks	3 (88.8)	Cisplatin (40 mg/m2/wk)	3DRT IMRT
Frikha	2018	III	NCT00828386 GORTEC2006-02	T2b-4N1-3	40	Mean (SD) 46 (10.2)	70	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 750 mg/m2/day, d1-5	3	Cisplatin (40 mg/m2/wk)	IMRT Non- IMRT
Hong	2018	III	NCT00201396	IVa-b 5th AJCC 97 UICC	239	45 (15-69)	73.6	Mitomycin C Epirubicin Cisplatin 5-Fluorouracil	8 mg/m2/day, d1 60 mg/m2/day, d1 60 mg/m2/day, d1 450 mg/m2/day, d8	3 (84.0)	Cisplatin (30 mg/m2/wk)	3DRT IMRT
Wei	2018	CS	-	T1-4N2-3 7th AJCC	693	-	74.9	Docetaxel Cisplatin or Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 or 80 mg/m2/day, d1 1000 mg/m2/day, d1-4	2 or 4	Cisplatin (40 mg/m2/wk or 80 mg/ m2/3wks)	IMRT Non- IMRT
Yang	2018	III	-	III–IVb 6th AJCC	212	(28-70)	69.3	Paclitaxel Cisplatin or Cisplatin 5-Fluorouracil	175 mg/m2/day, d1 75 mg/m2/day, d1 or 75 mg/m2/day, d1 1000 mg/m2/day, d1-4	2 (94.8)	Cisplatin (40 mg/m2/wk)	IMRT

Frontiers in Oncology

10.3389/fonc.2022.927510

Author	Year	Phase	Register number	Stage	No. P	Median age (range)	Male (%)	Regimens	Doses	Cycles (%)	CC	RT
Ghosh- Laskar	2019	_	_	II-IVb 6th AJCC	201	42 (18-73)	72.5	Paclitaxel Ifosfamide Cisplatin or Docetaxel Cisplatin 5-Fluorouracil	175 mg/m2/day, d1 1200 mg/m2/day, d1-5 15 mg/m2/day, d2-6 or 75 mg/m2/day, d1 75 mg/m2/day, d1 750 mg/m2/day, d1-5	2 or 3	Cisplatin (30 mg/m2/wk)	IMRT
Jin	2019	NIS	NCT01536223	III-IV 7th AJCC	138	48 (18-68)	71.7	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 600 mg/m2/day, d1-4	3	Cisplatin (80 mg/m2/3wks)	IMRT
					138	50 (25-69)	71	Cisplatin 5-Fluorouracil	100 mg/m2/day, d1 800 mg/m2/day, d1-5			
Lu	2019	NIS	ChiCTR-OIC-16008201	III-IVa 08 Chinese stage	60	45 (22-68)	85	Docetaxel Cisplatin 5-Fluorouracil	75 mg/m2/day, d1 75 mg/m2/day, d1 750 mg/m2/day, d1-5	2	Cisplatin (80 mg/m2/3wks)	IMRT
Zhang	2019	III	NCT01872962	III to IVb 7th AJCC	239	46 (18-64)	75.2	Gemcitabine Cisplatin	1 g/m2/day, d1+8 80 mg/m2/day, d1	3 (96.7)	Cisplatin (100 mg/m2/3wks)	IMRT
Zhao	2019	П	NCT03283293	III to IVb 6th AJCC	112	42 (14-68)	75	Cisplatin 5-Fluorouracil or Carboplatin Paclitaxel	80 mg/m2/day, d1 3.5 g/m2, d1-3 or AUC = 6, d1 135 mg/m2/day, d1	2 (100)	Cisplatin (80 mg/m2/3wks)	IMRT
Al-Rajhi	2020	II-III	NCT 03890185	III to IVb 7th AJCC	108	44 (19-70)	75.9	Docetaxel Cisplatin	75 mg/m2/day, d1 75 mg/m2/day, d1	2	Cisplatin (25 mg/m2/d1-4/wks)	IMRT
Li	2020	II	-	III to IVb 7th AJCC	58	47 (24-63)	72.4	Docetaxel Cisplatin	75 mg/m2/day, d1 80 mg/m2/day, d1	2 (89.7)	Cisplatin (80 mg/m2/3wks)	IMRT
Lv	2021	NIS III	ChiCTR-TRC-13003285	III to IVb 7th UICC	252	43.5 (36-50)	72.2	Lobaplatin 5-Fluorouracil	30 mg/m2/day, d1 800 mg/m2/day, d1-5	2	Lobaplatin (30 mg/m2/3wks)	IMRT
					250	44 (36-51)	72	Cisplatin 5-Fluorouracil	100 mg/m2/day, d1 800 mg/m2/day, d1-5	2	Cisplatin (100 mg/m2/3wks)	
Yao	2021	CS	_	III to IVb 7th AJCC/ UICC	182	-	80.2	Paclitaxel Platinum <sup>#</sup> 5-Fluorouracil or Paclitaxel Platinum <sup>#</sup> or Platinum <sup>#</sup> 5-Fluorouracil	210 mg/m2/day, d1 40 mg/m2/day, d1-3 750 mg/m2/day, d1-3 or 210 mg/m2/day, d1 40 mg/m2/day, d1-3 or 40 mg/m2/day, d1-3 750 mg/m2/day, d1-3	1 to 4	Platinum <sup>#</sup> (40 mg/m2/d1-3/3wks)	3DRT IMRT

No. P, number of patients; CC, concurrent chemotherapy; NIS, non-inferiority study; CS, cohort study; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer; 2DRT, two-dimensional radiotherapy; 3DRT, three-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy; Platinum<sup>#</sup>, cisplatin or nedaplatin; \*, included two trials.

	Study	Total		Rate	95%-CI	Weight
	Ferrari-2008	34		0.80	[0.65; 0.92]	2.9%
	Bac-2009	33		0.86	[0.72; 0.96]	2.9%
	Huang-2009 Hui-2009	201 34		0.76 0.94	[0.70; 0.82] [0.83; 1.00]	4.0% 2.9%
	Zheng-2010	54 60		0.94	[0.83; 1.00] [0.75; 0.93]	3.4%
	Fountzilas-2012	72		0.67	[0.55; 0.77]	3.5%
	Kong-2013	116	-	0.92	[0.87; 0.97]	3.8%
	Lim-2013	28		0.89	[0.75; 0.99]	2.7%
	Zhong-2013	46		0.94	[0.85; 0.99]	3.2%
	Rosenblatt-2014	139		0.63	[0.55; 0.71]	3.9%
	Lee-arm 1-2015/2020	161		0.65	[0.57; 0.72]	3.9%
	Lee-arm 2-2015/2020 Tan-2015	165		0.91	[0.86; 0.95]	3.9%
	1an-2015 Lv-arm 1-2016	86 44		0.94 0.72	[0.88; 0.98] [0.58; 0.85]	3.6% 3.1%
	Lv-arm 1-2016 Lv-arm 2-2016	44		0.72	[0.58; 0.85] [0.69; 0.92]	3.1%
	Sun/Li-2016/2019	241		0.92	[0.88; 0.95]	4.1%
	Tang-arm 1-2016	113		0.88	[0.81; 0.93]	3.8%
	Tang-arm 2-2016	110		0.86	[0.79; 0.92]	3.8%
	Cao/Yang-2017/2019	238		0.89	[0.84; 0.92]	4.1%
	Ke1-2017	36		0.92	[0.80; 0.99]	2.9%
	Ke2-2017	59	· · · · · ·	0.95	[0.88; 0.99]	3.4%
	Kong-2017	116		0.95	[0.89; 0.98]	3.8%
	Yang-2018 Ghosh-Laskar-2019	212 201		0.85 0.87	[0.80; 0.89] [0.82; 0.92]	4.0% 4.0%
	Jin-arm 1-2019	138	÷	0.91	[0.86; 0.95]	3.9%
	Jin-arm 2-2019	138	<u> </u>	0.91	[0.86; 0.95]	3.9%
	Zhang-2019	239	: +	0.96	[0.93; 0.98]	4.1%
	Al-Rajhi-2020	108		0.94	[0.88; 0.98]	3.7%
	Random effects model	3212	-	0.87	[0.84; 0.90]	100.0%
	Heterogeneity: $I^2 = 87\%$ , $t^2 = 0$ .	0142 , p < 0.01	0.6 0.7 0.8 0.9			
FFS		34		0.54	10 37-0 713	2.3%
	Ferrari-2008 Bae-2009	34 33		0.54	[0.37; 0.71] [0.59; 0.89]	2.3%
	Huang-2009	201		0.76	[0.63; 0.76]	4.7%
	Hui-2009	34		0.88	[0.75; 0.97]	2.3%
	Zheng-2010	60		0.75	[0.63; 0.85]	3.2%
	Fountzilas-2012	72		0.64	[0.53; 0.75]	3.4%
	Kong-2013	116		0.82	[0.74; 0.89]	4.1%
	Lim-2013	28		0.82	[0.65; 0.94]	2.1%
	Zhong-2013	46		0.73	[0.59; 0.85]	2.8%
	Rosenblatt-2014 Lee-arm 1-2015/2020	139 161		0.60 0.79	[0.52; 0.68] [0.72; 0.85]	4.3% 4.5%
	Lee-arm 2-2015/2020	165	-	0.81	[0.75; 0.87]	4.5%
	Tan-2015	86		0.75	[0.65; 0.84]	3.7%
	Lv-arm 1-2016	44		0.64	[0.49; 0.77]	2.7%
	Lv-arm 2-2016	44		0.70	[0.56; 0.83]	2.7%
	Sun/Li-2016/2019	241		0.80	[0.75; 0.85]	4.9%
	Tang-arm 1-2016	113		0.78	[0.69; 0.85]	4.1%
	Tang-arm 2-2016	110		0.75	[0.66; 0.83]	4.0%
	Cao/Yang-2017/2019 Ke1-2017	238 36		0.81 0.86	[0.76; 0.86] [0.73; 0.96]	4.9% 2.4%
	Ke2-2017 Ke2-2017	59		0.86	[0.72; 0.98]	3.1%
	Kong-2017	116	<u> </u>	0.82	[0.74; 0.88]	4.1%
	Yang-2018	212		0.79	[0.74; 0.85]	4.8%
	Ghosh-Laskar-2019	201		0.72	[0.66; 0.78]	4.7%
	Jin-arm 1-2019	138	: <del></del>	0.84	[0.78; 0.90]	4.3%
	Jin-arm 2-2019	138	<u> </u>	0.78	[0.71; 0.84]	4.3%
	Zhang-2019	239		0.86	[0.82; 0.90]	4.9%
			📥	0.77	[0.74; 0.80]	100.0%
	Random effects model	3104				
	Heterogeneity: $I^2 = 68\%$ , $t^2 = 0$ .		0.4 0.5 0.6 0.7 0.8 0.9			
LRF	Heterogeneity: $I^2 = 68\%$ , $t^2 = 0$ .	0047 , p < 0.01	0.4 0.5 0.6 0.7 0.8 0.9	0.88	[0.83: 0.921	6.6%
LRF	Heterogeneity: $I^2 = 68\%$ , $t^2 = 0$ .			0.88	[0.83; 0.92] [0.93; 1.00]	6.6% 6.1%
LRF	Heterogeneity: I <sup>2</sup> = 68%, t <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013	201 201 116 28		0.97 0.93	[0.93; 1.00] [0.80; 1.00]	6.1% 4.1%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, t <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Rosenblatt-2014	201 116 28 139		0.97 0.93 0.60	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68]	6.1% 4.1% 6.3%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, t <sup>2</sup> = 0. Huang-2009 Kong-2013 Rosemblatt-2014 Lv-arm 1-2016	201 116 28 139 44		0.97 0.93 0.60 0.88	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96]	6.1% 4.1% 6.3% 4.9%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, t <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Rosenblatt-2014 Lv-arm 1-2016 Lv-arm 2-2016	201 116 28 139 44 44		0.97 0.93 0.60 0.88 0.93	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99]	6.1% 4.1% 6.3% 4.9% 4.9%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hunap=2009 Kong=2013 Lim=2013 Rosenblatt=2014 Lv=arm 1=2016 Lv=arm 1=2016 SumLi=2016/2019	201 116 28 139 44		0.97 0.93 0.60 0.88	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95]	6.1% 4.1% 6.3% 4.9%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, t <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Rosenblatt-2014 Lv-arm 1-2016 Lv-arm 2-2016	201 116 28 139 44 44 241		0.97 0.93 0.60 0.88 0.93 0.92	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99]	6.1% 4.1% 6.3% 4.9% 4.9% 6.7%
LRF	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Lim-2013 Liw-arm 1-2016 Liv-arm 1-2016 Sum/Li-2016/2019 Tang-arm 1-2016	201 201 116 28 139 44 44 241 113		0.97 0.93 0.60 0.88 0.93 0.92 0.92	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96]	6.1% 4.1% 6.3% 4.9% 6.7% 6.7%
LRF	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Rosenblatt-2014 Liw-arm 2-2016 Sun (1-2016/2019) Tang-arm 1-2016 Cao'Nang-2017/2019 Kel-2017	201 201 116 28 139 44 44 44 241 113 110 238 36		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.92 0.93 0.97	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.88; 1.00]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.1%
LRF	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0 Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-ram 2-2016 Liw-ram 2-2016 Sam J-2016/2019 Tang-ram 2-2016 Cao/Yang-2016/2019 Kel-2017 Kel-2017	201 201 116 28 139 44 44 44 241 113 110 238 36 59		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.88; 1.00] [0.90; 1.00]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.1% 6.7% 4.5% 5.3%
LRF	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Huung-2009 Kong-2013 Lim-2013 Lim-2014 Liw-arm 2-2016 Sum/Li-2016/2019 Tang-arm 1-2016 Tang-arm 2-2016 Kal-2017 Kal-2017 Kal-2017	201 201 116 28 139 44 44 241 113 110 238 36 59 116		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.96	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.88; 1.00] [0.90; 1.00] [0.92; 0.99]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-arm 1-2016 Liw-arm 2-2016 SmL1-2016/2019 SmL1-2016/2019 SmL1-2016/2019 Kel-2017 Kel-2017 Keng-2017 Keng-2017 SmL2-2017	201 201 116 28 139 44 44 241 113 110 238 36 59 116 212		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.96 0.93	[0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.88; 0.96] [0.88; 1.00] [0.90; 1.00] [0.92; 0.99] [0.89; 0.96]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1% 6.6%
LRF	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Lim-2013 Lim-2014 Lix-arm 2-2016 Sun/Li-2016/2019 Tang-arm 1-2016 Tang-arm 1-2016 Cao/Yang-2017 Ke2-2017 Ke2-2017 Keng-2017 Yang-2018 Ghoba-Laskar-2019	201 201 116 28 139 44 44 241 113 110 238 36 59 116 59 116 212 201		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.96 0.93 0.85	0.93; 1.00] [0.80; 1.00] [0.52; 0.68] [0.76; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.89; 0.96] [0.90; 1.00] [0.92; 0.99] [0.89; 0.96] [0.80; 0.90]	$\begin{array}{c} 6.1\% \\ 4.1\% \\ 6.3\% \\ 4.9\% \\ 4.9\% \\ 6.7\% \\ 6.1\% \\ 6.1\% \\ 5.3\% \\ 6.1\% \\ 6.6\% \\ 6.6\% \end{array}$
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-arm 1-2016 Liw-arm 2-2016 SmL1-2016/2019 SmL1-2016/2019 SmL1-2016/2019 Kel-2017 Kel-2017 Keng-2017 Keng-2017 SmL2-2017	201 201 116 28 139 44 44 241 113 110 238 36 59 116 212		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.96 0.93	0.93; 1.00] [0.80; 1.00] [0.80; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.89; 0.96] [0.99; 1.00] [0.92; 0.99] [0.89; 0.96] [0.80; 0.90] [0.89; 0.96]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1% 6.6%
LRF	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Huung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-arm 1-2016 Liw-arm 2-2016 SunLi-2016(2019) Tang-arm 1-2016 Cas'mag-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kong-2018 Ghosh-Laskar-2019 Zhang-2019 Al-Rajhi-2020	201 116 28 139 44 44 241 113 110 238 36 59 116 212 201 201 201 201 201 201		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.96 0.93 0.85 0.93 0.86	$\begin{matrix} [0.93; 1.00]\\ [0.80; 1.00]\\ [0.52; 0.68]\\ [0.76; 0.96]\\ [0.83; 0.99]\\ [0.88; 0.95]\\ [0.86; 0.96]\\ [0.88; 1.00]\\ [0.89; 0.96]\\ [0.88; 1.00]\\ [0.92; 0.99]\\ [0.89; 0.96]\\ [0.80; 0.90]\\ [0.89; 0.96]\\ [0.79; 0.92]\end{matrix}$	$\begin{array}{c} 6.1\% \\ 4.1\% \\ 6.3\% \\ 4.9\% \\ 4.9\% \\ 6.7\% \\ 6.1\% \\ 6.1\% \\ 6.7\% \\ 4.5\% \\ 5.3\% \\ 6.6\% \\ 6.6\% \\ 6.6\% \\ 6.7\% \\ 6.0\% \\ 6.0\% \end{array}$
LRFS	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-arm 1-2016 Liw-arm 2-2016 SunLi-2016(2019) Tang-arm 1-2016 Cas'Ing-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kong-2017 Song-2018 Ghosh-Laskar-2019 Zhang-2019	201 116 28 139 44 44 241 113 110 238 36 59 116 212 201 201 201 201 201 8 59 116 212 201 201 201 201 201 203 205 204 205 201 205 205 205 205 205 205 205 205 205 205		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.93 0.85 0.93	0.93; 1.00] [0.80; 1.00] [0.80; 0.96] [0.83; 0.99] [0.88; 0.95] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.89; 0.96] [0.99; 1.00] [0.92; 0.99] [0.89; 0.96] [0.80; 0.90] [0.89; 0.96]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.1% 6.7% 6.1% 6.6% 6.6% 6.6%
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Hunng-2009 Kong-2013 Lim-2013 Rossenbilt: 2014 Lv-arm 1-2016 Lv-arm 2-2016 Sam (L-2016/2019) Tang-arm 1-2016 Tang-arm 2-2016 Caso/Yang-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Keng-2018 Ghosh-Laskar-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , 1 <sup>2</sup> = 0	201 116 28 139 44 44 44 113 110 238 36 59 116 212 201 239 108 2245 0112 , p < 0.01		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.96 0.93 0.85 0.93 0.85	$\begin{matrix} [0.93; 1.00]\\ [0.80; 1.00]\\ [0.52; 0.63\\ [0.76; 0.96]\\ [0.76; 0.96]\\ [0.83; 0.97]\\ [0.86; 0.96]\\ [0.86; 0.96]\\ [0.88; 0.96]\\ [0.88; 1.00]\\ [0.89; 0.96]\\ [0.80; 0.99]\\ [0.80; 0.90]\\ [0.80; 0.90]\\ [0.80; 0.96]\\ [0.79; 0.92]\\ [0.87; 0.94] \end{matrix}$	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1% 6.6% 6.6% 6.6% 6.0%
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0 Hung-2009 Kong-2013 Lim-2013 Lim-2013 Rosenblatt-2014 Low-arm 2-2016 Sun Ji-2016 2019 Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 2-2016 Kal-2017 Kong-2017 Kong-2017 Kong-2017 Kong-2018 Ghoh-Lakkar-2019 Zhang-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , 1 <sup>2</sup> = 0 Hung-2009	201 116 28 139 44 44 241 113 110 238 36 59 116 212 201 201 201		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.92 0.97 0.97 0.97 0.93 0.85 0.93 0.85 0.93 0.86 0.91	[0.33; 1.00] [0.30; 1.00] [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.56; 0.96] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.89; 0.96] [0.90; 1.00] [0.90; 1.00] [0.90; 0.90] [0.89; 0.96] [0.79; 0.92] [0.87; 0.94]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1% 6.6% 6.6% 6.6% 6.7% 6.0%
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Hunng-2009 Kong-2013 Lim-2013 Rossenbilt: 2014 Lv-arm 1-2016 Lv-arm 2-2016 Sam (L-2016/2019) Tang-arm 1-2016 Tang-arm 2-2016 Caso/Yang-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Keng-2018 Ghosh-Laskar-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , 1 <sup>2</sup> = 0	201 116 28 139 44 44 44 113 110 238 36 59 116 212 201 239 108 2245 0112 , p < 0.01		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.96 0.93 0.85 0.93 0.85	[0.35; 1.00] [0.52; 0.68 [0.52; 0.68 [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.58; 0.96] [0.58; 0.96] [0.58; 0.96] [0.58; 0.96] [0.58; 0.96] [0.58; 0.96] [0.59; 0.96] [0.59; 0.96] [0.59; 0.96] [0.59; 0.96] [0.59; 0.96] [0.79; 0.92] [0.79; 0.94]	6.1% 4.1% 6.3% 4.9% 6.7% 6.1% 6.7% 4.5% 5.3% 6.1% 6.6% 6.6% 6.6% 6.0%
	Heterogeneity: 1 <sup>2</sup> = 68% , t <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Lv-arm 1-2016 Lv-arm 2-2016 SunLi-2016/2019 SunLi-2016/2019 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Keng-2018 Ghosh-Laskar-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , t <sup>2</sup> = 0 Hung-2009 Kong-2013	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 241\\ 113\\ 110\\ 2.88\\ 36\\ 59\\ 116\\ 212\\ 201\\ 239\\ 108\\ 2245\\ 0112\ , p < 0.01\\ \end{array}$		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.93 0.85 0.93 0.85 0.93 0.86 0.91	[0.33; 1.00] [0.30; 1.00] [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.56; 0.96] [0.86; 0.96] [0.86; 0.96] [0.89; 0.96] [0.89; 0.96] [0.90; 1.00] [0.90; 1.00] [0.90; 0.90] [0.89; 0.96] [0.79; 0.92] [0.87; 0.94]	6.1% 4.1% 6.3% 4.9% 6.7% 6.7% 6.7% 6.7% 6.6% 6.6% 6.0% 100.0% 6.8% 6.3%
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0 Huang-2009 Keng-2013 Lim-2013 Rosenblatt-2014 Lv-arm 1-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Sam Li-2016 Kel-2017 Kel-2017 Kang-2018 Ghoha-Laskar-2019 Zhang-2019 Al-Espii-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hang-2009 Keng-2013 Rosenblatt-2014	0047 , p < 0.01 201 116 28 139 44 44 241 13 110 238 36 59 116 212 201 201 201 108 2245 0112 , p < 0.01		0.97 0.93 0.660 0.88 0.92 0.92 0.92 0.93 0.97 0.96 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.92 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.92 0.95 0.95 0.95 0.95 0.95 0.95 0.95 0.95	[0.33; 1.00] [0.32; 0.68] [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.52; 0.68] [0.52; 0.56] [0.58; 0.95] [0.58; 0.96] [0.58; 0.96] [0.90; 1.00] [0.90; 1.00] [0.90; 1.00] [0.90; 0.90] [0.59; 0.96] [0.79; 0.92] [0.87; 0.94] [0.70; 0.81] [0.53; 0.94] [0.51; 0.68]	6.1% 4.1% 6.3% 4.9% 4.9% 6.7% 6.1% 6.1% 6.7% 6.7% 6.7% 6.0% 100.0% 6.8% 6.3% 6.3% 6.5%
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Lv-arm 1-2016 Lv-arm 2-2016 SunLi-2016(2019) Tang-arm 1-2016 Losen'Jang-2016 SunLi-2016(2019) Kal-2017 Kel-2017	0047 , p < 0.01 201 116 28 139 44 44 241 113 110 2.88 39 116 212 201 239 108 2245 0112 , p < 0.01 201 116 139 86 44 241		0.97 0.93 0.66 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.97 0.93 0.85 0.93 0.85 0.93 0.86 0.91 0.76 0.89 0.60 0.84 0.73 0.97	$\begin{array}{c} [0.35; 1.00] \\ [0.52; 0.68] \\ [0.52; 0.68] \\ [0.52; 0.68] \\ [0.53; 0.99] \\ [0.83; 0.95] \\ [0.84; 0.95] \\ [0.84; 0.96] \\ [0.84; 0.96] \\ [0.84; 0.96] \\ [0.84; 0.96] \\ [0.84; 0.96] \\ [0.92; 0.99] \\ [0.93; 0.94] \\ [0.51; 0.68] \\ [0.55; 0.91] \\ [0.85; 0.93] \\ [0.85; 0.85] \\$	6.1% 4.1% 6.3% 4.9% 4.9% 6.7% 6.1% 6.7% 6.1% 6.7% 6.1% 6.6% 6.6% 6.0% 100.0% 6.3% 6.3% 6.3% 6.3% 6.9% 5.0% 6.9%
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Huang-2009 Kong-2013 Lim-2013 Rowenbiat-2014 Lv-arm 2-2016 Sam (J-2016) Sam (J-2016) Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 2-2016 Kel-2017 Kel-2017 Kong-2017 Kamg-2018 Ghodb-Laskar-2019 Zhang-2019 And-Bajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , 1 <sup>2</sup> = 0 Huang-2009 Kong-2013 Rosenblat-2016 Sam (J-2016) Sam (J-2016)	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 241\\ 13\\ 110\\ 238\\ 36\\ 59\\ 116\\ 212\\ 201\\ 239\\ 108\\ 2245\\ 0112 \ , p < 0.01\\ \hline \end{array}$		0.97 0.93 0.66 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.96 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.85 0.93 0.95 0.95 0.95 0.95 0.95 0.95 0.95 0.95	$\begin{array}{c} [0.35; 1.00] \\ [0.52; 0.68] \\ [0.52; 0.68] \\ [0.52; 0.68] \\ [0.52; 0.68] \\ [0.53; 0.99] \\ [0.83; 0.95] \\ [0.86; 0.96] \\ [0.86; 0.96] \\ [0.86; 0.96] \\ [0.88; 1.00] \\ [0.92; 0.99] \\ [0.88; 0.96] \\ [0.92; 0.99] \\ [0.89; 0.96] \\ [0.79; 0.92] \\ [0.87; 0.94] \\ \hline \end{array}$	6.1% 4.1% 6.3% 4.9% 4.9% 6.7% 6.1% 6.1% 6.1% 5.3% 6.6% 6.6% 6.6% 6.6% 6.6% 6.6% 6.6% 6
LRFS	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Liw-arm 1-2016 Liw-arm 2-2016 Sund 1:-2016(2019) Tang-arm 1-2016 Liw-arm 2-2016 Sund 1:-2016(2019) Tang-arm 2-2016 Caso <sup>1</sup> Tang-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Keng-2018 Random effects model Huang-2009 Kong-2013 Rosenblat: 2014 Tan-2015 Liw-arm 2-2016 Sunf.1-2016(2019) Tang-arm 1-2016	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 241\\ 113\\ 10\\ 238\\ 36\\ 59\\ 116\\ 212\\ 201\\ 239\\ 108\\ 212\\ 201\\ 239\\ 108\\ 116\\ 116\\ 119\\ 108\\ 86\\ 44\\ 113\\ 110\\ 110\\ 110\\ 110\\ 110\\ 110\\ 110$		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.96 0.93 0.85 0.93 0.85 0.93 0.86 0.91 0.76 0.80 0.84 0.73 0.84 0.73 0.90 0.85	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.53, 0.99] \\ [0.38, 0.95] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.59, 0.96] \\ [0.59, 0.96] \\ [0.59, 0.96] \\ [0.59, 0.96] \\ [0.59, 0.96] \\ [0.59, 0.96] \\ [0.79, 0.92] \\ [0.79, 0.92] \\ [0.77, 0.94] \\ \hline \end{array}$	6.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 4.9% 4.9% 6.1% 6.1% 6.1% 6.6% 6.6% 6.6% 6.6% 6.6
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat-2014 Lv-arm 2-2016 Lv-arm 2-2016 Sun (J-2016/2019) Tang-arm 1-2016 Tang-arm 2-2016 Cao/Yang-2017/019 Kel-2017 Kel-201	0047 , p < 0.01 201 116 28 139 44 241 13 10 238 36 59 116 212 201 2245 0112 , p < 0.01 2245 0112 , p < 0.01 116 139 86 44 241 113 110 238 36 212 201 238 239 108 212 239 108 212 239 108 212 239 108 212 239 108 212 239 108 212 239 108 212 239 108 212 238 201 116 116 116 118 119 212 201 118 110 238 201 118 110 212 201 118 118 110 212 201 108 109 108 212 201 108 201 108 212 201 108 212 201 108 201 201 108 201 201 201 201 201 201 201 201		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.93 0.97 0.96 0.93 0.85 0.88 0.93 0.86 0.91 0.60 0.89 0.60 0.84 0.89 0.64 0.89 0.64 0.84 0.85 0.85	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.36, 1.00] \\ [0.37, 0.96] \\ [0.37, 0.96] \\ [0.38, 0.97] \\ [0.38, 0.97] \\ [0.38, 0.96] \\$	6.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 6.1% 5.1% 6.1% 6.1% 6.1% 6.1% 6.6% 6.7% 6.0% 6.3% 6.0% 6.3% 6.3% 6.3% 6.3%
	$\begin{split} & \text{Heterogeneity: } l^2 = 68\%, l^2 = 0. \\ & \text{Humg-2009} \\ & \text{Kong-2013} \\ & \text{Lim-2013} \\ & \text{Rowenbilt-2014} \\ & \text{Ly-arm 1-2016} \\ & \text{Karl, 2-016} \\ & \text{Karl, 2-016} \\ & \text{Karl, 2-016} \\ & \text{Karl, 2-017} \\ & \text{Karl, 2-016} \\ & \text{Lamg-2019} \\ & \text{Lamg-2019} \\ & \text{Random effects model} \\ & \text{Heterogeneity: } l^2 = 85\%, l^2 = 0 \\ & \text{Hamg-2009} \\ & \text{Random effects model} \\ & \text{Haterogeneity: } l^2 = 85\%, l^2 = 0 \\ & \text{Lymg-2017} \\ & \text{Karl, 2-016} \\ & \text{Lymg-2017} \\ & \text{Karl, 2-016} \\ & \text{Cano'Marg-2017} \\ & \text{Karl, 2-016} \\ & \text{Cano'Marg-2017} \\ & \text{Karl, 2-016} \\ & \text{Cano'Marg-2017} \\ & \text{Karl, 2-016} \\ & \text{Karl, 2-017} \\ & \text{Karl, 2-016} \\ & Karl, 2$	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 143\\ 133\\ 139\\ 241\\ 113\\ 101\\ 238\\ 36\\ 59\\ 116\\ 212\\ 201\\ 239\\ 108\\ 212\\ 201\\ 108\\ 116\\ 119\\ 108\\ 116\\ 139\\ 86\\ 44\\ 113\\ 118\\ 138\\ 36\\ \end{array}$		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.95 0.93 0.83 0.83 0.83 0.83 0.84 0.91 0.76 0.84 0.73 0.84 0.73 0.85 0.85	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.53, 0.99] \\ [0.38, 0.95] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.58, 0.96] \\ [0.59, 0.96] \\$	6.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 4.9% 4.9% 6.1% 6.1% 6.1% 6.6% 6.6% 6.6% 6.6% 6.3% 6.3% 6.3% 6.3
	Heterogeneity: 1 <sup>2</sup> = 68% , 1 <sup>2</sup> = 0. Hung-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Lv-arm 1-2016 Lv-arm 2-2016 Sam (1-2016 2019) Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 2-2016 CacyYang-2018 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85% , 1 <sup>2</sup> = 0 Hung-2009 Kong-2013 Rosenblat: 2014 Tang-2015 Sam (1-2016 2019) Tang-arm 2-2016 Sam (1-2016 2019) Tang-arm 2-2016 Sam (1-2017 2019) Kel-2017	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 113\\ 110\\ 28\\ 36\\ 69\\ 116\\ 212\\ 201\\ 239\\ 108\\ 212\\ 201\\ 108\\ 212\\ 201\\ 108\\ 108\\ 108\\ 108\\ 139\\ 0112, p < 0.01\\ \hline \end{array}$		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.96 0.93 0.85 0.93 0.85 0.93 0.86 0.91 0.76 0.89 0.64 0.89 0.84 0.87 0.87 0.85 0.85 0.86	$\begin{array}{c} [0.35, 1.00]\\ [0.80, 1.00]\\ [0.52, 0.68]\\ [0.76, 0.96]\\ [0.76, 0.96]\\ [0.53, 0.99]\\ [0.58, 0.95]\\ [0.58, 0.95]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.58, 0.96]\\ [0.79, 0.92]\\ [0.58, 0.96]\\ [0.79, 0.92]\\ [0.57, 0.94]\\ \hline \\ [0.70, 0.81]\\ [0.58, 0.96]\\ [0.75, 0.94]\\ [0.58, 0.85]\\ [0.58, 0.85]\\ [0.58, 0.85]\\ [0.58, 0.92]\\ [0.58, 0.92]\\ [0.58, 0.92]\\ [0.58, 0.91]\\ [0.58, 0.91]\\ [0.58, 0.97]\\ [0.58$	6.1% 6.1% 4.1% 6.1% 6.3% 6.7% 6.1% 6.1% 6.1% 6.1% 6.1% 6.7% 6.3% 6.3% 6.3% 6.3% 6.5% 6.5% 6.5% 6.5% 6.5% 6.3% 6.5% 6.5% 6.5% 6.5% 6.5% 6.5% 6.5% 6.5
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung=2009 Kong=2013 Lim=2013 Rosenblat: 2014 Liw=arm 1-2016 Liw=arm 1-2016 Liw=arm 1-2016 Cas Yang=2017(2019 Kel=2017 Kong=2017(2019 Kel=2017 Kong=2017 Jang=2019 Al=Rajhi=2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hung=2019 Al=Rajhi=2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hung=2019 Rosenblat: 2014 Tan=2015 Liw=arm 2-2016 Cas/Yang=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017	0047 , p < 0.01 201 116 28 139 44 44 44 113 110 238 36 59 116 122 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 218 201 239 108 212 201 218 218 218 218 218 218 218 21		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.96 0.93 0.85 0.93 0.85 0.91 0.76 0.89 0.60 0.89 0.60 0.84 0.73 0.85 0.85 0.85 0.85 0.85	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.53, 0.99] \\ [0.38, 0.95] \\ [0.38, 0.95] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.57, 0.94] \\ \hline \\ [0.77, 0.94] \\ \hline \\ [0.77, 0.94] \\ \hline \\ [0.57, 0.94] \\ [0.57, 0.94] \\ [0.57, 0.94] \\ [0.57, 0.91] \\ [0.58, 0.93] \\ [0.57, 0.91] \\ [0$	6.1% 4.1% 4.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 4.9% 4.5% 6.1% 6.7% 6.7% 4.5% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Humg-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Ly-arm 1-2016 Ly-arm 2-2016 Sam (L-2016/2019) Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 2-2016 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Huag-2009 Kong-2013 Rosenblat: 2014 Ly-arm 2-2016 Tang-arm 1-2016 Tang-arm 2-2016 Tang-arm 2-2016 Cao'Yang-2017/2019 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017	201 116 28 139 44 44 44 113 110 28 36 59 116 212 201 239 108 2245 0112 , p < 0.01 201 116 139 001 201 201 201 201 201 201 201		0.97 0.93 0.660 0.88 0.93 0.92 0.92 0.92 0.92 0.92 0.92 0.93 0.95 0.85 0.95	$\begin{array}{c} [0.35, 1.00]\\ [0.80, 1.00]\\ [0.50, 1.00]\\ [0.50, 20, 68]\\ [0.76, 0.96]\\ [0.76, 0.96]\\ [0.56, 0.96]\\ [0.36, 0.96]\\ [0.36, 0.96]\\ [0.36, 0.96]\\ [0.36, 0.96]\\ [0.38, 0.91]\\ [0.38, $	6.1% 4.1% 4.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 4.9% 4.9% 4.9% 4.9% 4.9
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Hung=2009 Kong=2013 Lim=2013 Rosenblat: 2014 Liw=arm 1-2016 Liw=arm 1-2016 Liw=arm 1-2016 Cas Yang=2017(2019 Kel=2017 Kong=2017(2019 Kel=2017 Kong=2017 Jang=2019 Al=Rajhi=2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hung=2019 Al=Rajhi=2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hung=2019 Rosenblat: 2014 Tan=2015 Liw=arm 2-2016 Cas/Yang=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017 Kel=2017	0047 , p < 0.01 201 116 28 139 44 44 241 113 10 238 36 59 116 122 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 239 108 212 201 218 201 239 108 212 201 218 218 218 218 218 218 218 21		0.97 0.93 0.60 0.88 0.92 0.92 0.92 0.93 0.97 0.97 0.97 0.96 0.93 0.85 0.93 0.85 0.91 0.76 0.89 0.60 0.89 0.60 0.84 0.73 0.85 0.85 0.85 0.85 0.85	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.52, 0.68] \\ [0.53, 0.99] \\ [0.38, 0.95] \\ [0.38, 0.95] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.38, 0.96] \\ [0.57, 0.94] \\ \hline \\ [0.77, 0.94] \\ \hline \\ [0.77, 0.94] \\ \hline \\ [0.57, 0.94] \\ [0.57, 0.94] \\ [0.57, 0.94] \\ [0.57, 0.91] \\ [0.58, 0.93] \\ [0.57, 0.91] \\ [0$	6.1% 4.1% 4.1% 4.1% 4.1% 4.1% 4.9% 4.9% 4.9% 4.9% 4.5% 6.1% 6.7% 6.7% 4.5% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7% 6.7
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Huang-2009 Keng-2013 Lim-2013 Rosenblatt-2014 Ly-arm 1-2016 Ly-arm 2-2016 Sun Li-2016/2019 Sun Li-2016/2019 Sun Li-2016/2019 Sun Li-2016/2019 Sun Li-2016/2019 Kel-2017 Keng-2017 Keng-2017 Keng-2019 Al-Explin-2019 Al-Explin-2019 Al-Explin-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0 Hang-2009 Keng-2017 Sun Li-2016/2019 Tang-arm 1-2016 Sun Li-2016/2019 Tang-arm 1-2016 Sun Li-2016/2019 Tang-arm 2-2016 Sun Li-2016/2019 Kel-2017 Ke2	$\begin{array}{c} 201\\ 116\\ 28\\ 139\\ 44\\ 44\\ 241\\ 13\\ 110\\ 238\\ 36\\ 59\\ 116\\ 238\\ 36\\ 59\\ 116\\ 212\\ 201\\ 108\\ 2245\\ 0112\ , p < 0.01\\ \hline \end{array}$		0.97 0.93 0.60 0.88 0.93 0.92 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.93 0.97 0.96 0.97 0.96 0.97 0.96 0.97 0.96 0.97 0.96 0.97 0.96 0.97 0.96 0.93 0.97 0.96 0.97 0.96 0.97 0.96 0.97 0.96 0.93 0.97 0.96 0.95 0.96 0.95 0.96 0.96 0.96 0.97 0.96 0.88 0.88 0.88 0.88 0.88 0.99 0.97 0.86 0.88 0.86 0.88 0.88 0.88 0.86 0.88 0.88 0.86 0.88 0.88 0.86 0.88 0.88 0.86 0.88 0.99 0.85 0.88 0.99 0.85 0.88 0.99 0.85 0.88 0.99 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.95	$\begin{array}{c} [0.35, 1.00] \\ [0.36, 1.00] \\ [0.36, 1.00] \\ [0.52, 0.68] \\ [0.76, 0.96] \\ [0.76, 0.96] \\ [0.37, 0.96] \\ [0.38, 0.95] \\ [0.38, 0.95] \\ [0.38, 0.96] \\$	6.1% 6.1% 4.1% 6.3% 6.3% 6.3% 6.7% 6.7% 5.3% 6.6% 6.6% 6.6% 6.3% 6.3% 6.3% 6.3% 6
	Heterogeneity: 1 <sup>2</sup> = 68%, 1 <sup>2</sup> = 0. Humg-2009 Kong-2013 Lim-2013 Rosenblat: 2014 Ly-arm 1-2016 Ly-arm 2-2016 Sun Li-2016/2019 Sun Li-2016/2019 Kal-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Kel-2017 Keng-2018 Alma-2019 Al-Rajhi-2020 Random effects model Heterogeneity: 1 <sup>2</sup> = 85%, 1 <sup>2</sup> = 0. Humg-2009 Kong-2013 Rosenblat: 2014 Tan-2015 Ly-arm 2-2016 Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 1-2016 Tang-arm 2-2016 Tang-arm 1-2016 Tang-arm 2-2016 Sun Li-2017 Kel	20047 , p < 0.01 201 116 28 139 44 44 44 113 110 238 36 59 116 212 201 239 108 2245 0112 , p < 0.01 201 116 139 86 44 41 113 110 238 36 59 116 212 201 239 108 59 116 119 24 201 239 108 59 116 212 201 139 108 59 116 212 201 239 108 59 116 212 201 239 108 59 116 212 201 239 108 59 116 212 201 239 108 59 116 212 201 239 108 59 116 212 201 239 108 59 116 139 108 245 59 116 139 139 108 2245 201 201 201 201 201 201 201 201		0.97 0.93 0.60 0.88 0.93 0.92 0.92 0.92 0.92 0.92 0.92 0.93 0.93 0.93 0.93 0.93 0.93 0.93 0.93	$\begin{array}{c} [0.35, 1.00]\\ [0.80, 1.00]\\ [0.50, 1.00]\\ [0.50, 20, 68]\\ [0.76, 0.96]\\ [0.53, 0.99]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.56, 0.96]\\ [0.57, 0.91]\\ [0.57, 0.91]\\ [0.57, 0.91]\\ [0.57, 0.91]\\ [0.57, 0.94]\\ \hline \end{array}$	6.1%4 4.1%5 6.3%4 4.9%5 4.9%5 6.7%5 6.7%5 6.1%5 6.1%5 6.1%5 6.6%5 6.6%5 6.6%5 6.6%5 6.6%5 6.3%5

FIGURE 1

Rates of 3-year overall survival (OS), failure-free survival (FFS), locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS).

	Study	Total		Rate	95%-CI	Weig
	Huang-2012/2015	201	:	0.70	[0.64; 0.76]	9.
	Lee-arm 1-2015/2020	161		0.84	[0.78; 0.89]	8.
	Lee-arm 2-2015/2020	165		0.83	[0.77; 0.89]	8.
	Lv-arm 1-2016	44	;;;	0.66	[0.51; 0.79]	6.
	Lv-arm 2-2016	44	<u>.</u>	0.70	[0.56; 0.83]	6.
	Sun/Li-2016/2019	241		0.86	[0.81; 0.90]	9.
	Cao/Yang-2017/2019	238		0.81	[0.76; 0.86]	9.3
	Kong-2017	116		0.87	[0.80; 0.93]	8.2
		239		0.87		8 9.3
	Hong-2018				[0.66; 0.78]	
	Li-2020	58		0.73	[0.61; 0.84]	6.1
	Lv-arm 1-2021	252		0.88	[0.84; 0.92]	9.3
	Lv-arm 2-2021	250		0.89	[0.85; 0.93]	9.3
	Random effects model	2009		0.81	[0.76; 0.85]	100.0
	Heterogeneity: $I^2 = 83\%$ , $t^2 = 0.00$	73 , $p \le 0.01$	0.6 0.7 0.8 0.9			
FF			0.0 0.7 0.8 0.9			
	Huang-2012/2015	201		0.62	[0.55; 0.69]	9.9
	Lee-arm 1-2015/2020	161		0.77	[0.70; 0.83]	9.3
	Lee-arm 2-2015/2020	165		0.78	[0.72; 0.84]	9.4
	Lv-arm 2-2016	44		0.66	[0.51; 0.79]	5.3
	Sun/Li-2016/2019	241		0.77	[0.72; 0.82]	10.3
	Cao/Yang-2017/2019	238		0.73	[0.68; 0.79]	10.
	Kong-2017	116		0.74	[0.66; 0.82]	8.
	Hong-2018	239		0.61	[0.55; 0.67]	10.
	Li-2020	58		0.80	[0.69; 0.89]	6.3
	Lv-arm 1-2021	252		0.75	[0.69; 0.80]	10.4
	Lv-arm 2-2021	250		0.76	[0.70; 0.81]	10.4
	D. MILL DODI	200	-	0170	found of order	101
	Random effects model Heterogeneity: I <sup>2</sup> = 73%, t <sup>2</sup> = 0.00	1965		0.73	[0.69; 0.77]	100.0
		38 , p < 0.01	0.55 0.6 0.65 0.7 0.75 0.8 0.85			
LRF	S Huang-2012/2015	201		0.85	[0.79; 0.89]	13.1
	Sun/Li-2016/2019	241		0.91	[0.87; 0.94]	14.1
	Cao/Yang-2017/2019	238		0.88	[0.83; 0.92]	14.1
	Kong-2017	116		0.90	[0.84; 0.95]	9.8
	Hong-2018	239		0.80	[0.75; 0.85]	14.1
	Li-2020	58		0.91	[0.82; 0.97]	6.2
				0.88	[0.83; 0.91]	14.4
	Lv-arm 1-2021	252				14.3
	Lv-arm 1-2021 Lv-arm 2-2021	252 250		0.89	[0.85; 0.92]	
				0.89	[0.85; 0.92]	100.0
	Lv-arm 2-2021	250 1595 15, p = 0.03				100.0
DMF	Lv–arm 2–2021 Random effects model $Heterogeneity: \ \ I^2 = 54\% \ , \ t^2 = 0.00$	250 1595 15, p = 0.03	0.75 0.8 0.85 0.9 0.95			100.0
DMF	$L\nu$ -arm 2–2021 Random effects model Heterogeneity: $T^2 = 54\%$ , $t^2 = 0.00$ 78 Huang–2012/2015	250 1595 15 , p = 0.03 201	0.75 0.8 0.85 0.9 0.95	0.87	[0.85; 0.90]	12.9
DMF	Lvarm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54%, 1 <sup>2</sup> = 0.00 'S Huang-2012/2015 Sun/Li-2016/2019	250 1595 15 , p = 0.03		0.87	[0.85; 0.90]	12.9
DMF	$L\nu$ -arm 2–2021 Random effects model Heterogeneity: $T^2 = 54\%$ , $t^2 = 0.00$ 78 Huang–2012/2015	250 1595 15 , p = 0.03 201		0.87	[0.85; 0.90]	12.9
DMF	Lvarm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54%, 1 <sup>2</sup> = 0.00 'S Huang-2012/2015 Sun/Li-2016/2019	250 1595 15 , p = 0.03 201 241		0.87	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92]	12. 13. 13.
DMF	Lv-arm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54%, 1 <sup>2</sup> = 0.00 'S Huang-2012/2015 Sun/Li-2016/2019 Cao/Yang-2017/2019	250 1595 15 , p = 0.03 201 241 238		0.87 0.70 0.88 0.83	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92] [0.78; 0.87]	12.9 13.1 13.1 11.0
DMF	Lv-arm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54% , 1 <sup>2</sup> = 0.00 78 Huang-2012/2015 Sun7.i-2016/2019 Cao'Yang-2017/2019 Kong-2017	250 1595 15 , p = 0.03 201 238 116		0.87 0.70 0.88 0.83 0.93	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92] [0.78; 0.87] [0.87; 0.97] [0.70; 0.81]	12.9 13.2 13.2 11.6 13.2
DMF	Lv-arm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54%, 1 <sup>2</sup> = 0.00 S Huang=2012/2015 Sum/Li-2016/2019 Cao/Yang=2017/2019 Kong=2017 Hong=2018	250 1595 15, p = 0.03 201 241 238 116 239		0.87 0.70 0.88 0.83 0.93 0.76	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92] [0.78; 0.87] [0.87; 0.97] [0.70; 0.81] [0.71; 0.91]	12.5 13.2 13.2 11.6 13.2 9.4
DMF	Lx-arm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 5496, 1 <sup>2</sup> = 0.00 YS Huang=2012/2015 Sum/Li-2016/2019 CanoYang=2017/2019 Kong=2017 Hong=2018 Li-2020	250 1595 15, p = 0.03 201 241 238 116 239 58		0.87 0.70 0.88 0.83 0.93 0.76 0.82	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92] [0.78; 0.87] [0.87; 0.97] [0.70; 0.81]	12.9 13.2 13.2 11.6 13.2 9,4 13.3
DMF	Lv-arm 2-2021 Random effects model Heterogeneity: 1 <sup>2</sup> = 54%, 1 <sup>2</sup> = 0.00 S Humag-2012/2015 Sun/Li-2016/2019 Cao Yang-2017/2019 Kong-2017 Hong-2018 Li-2020 Lv-arm I-2021	250 1595 15 , p = 0.03 201 241 241 238 116 239 58 252		0.87 0.70 0.88 0.83 0.93 0.76 0.82 0.87	[0.85; 0.90] [0.63; 0.76] [0.84; 0.92] [0.78; 0.87] [0.87; 0.97] [0.70; 0.81] [0.70; 0.81] [0.72; 0.91]	100.09 12.99 13.29 13.29 13.29 13.29 13.29 13.39 13.39

FIGURE 2

Rates of 5-year overall survival (OS), failure-free survival (FFS), locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS).

post CCRT: 99% [95% CI, 97%-100%] vs. 83% [95% CI, 74%-91%]) versus patients outside Chinese region.

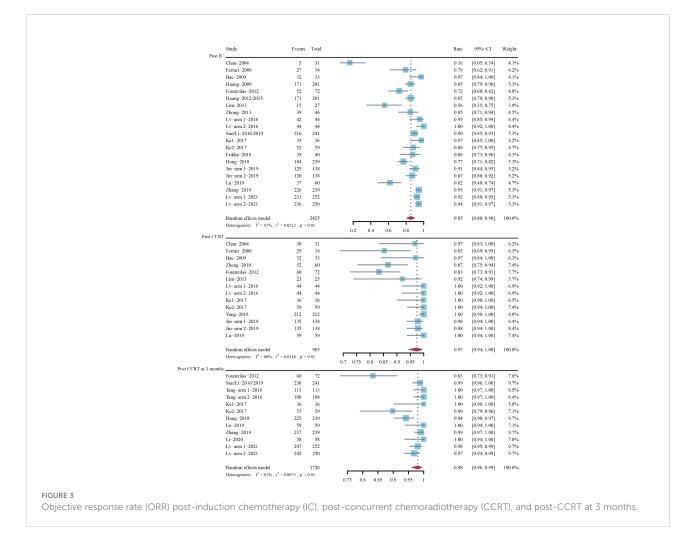
GP induction chemotherapy was associated with the highest 3-year OS and FFS rates (OS: 94% [95% CI, 87%-99%]; FFS: 86% [82%-90%]), followed by TPF (92% [95% CI, 90%-94%]; 82% [78%-85%]), TP (89% [95% CI, 84%-93%]; 77% [71%-83%]), and PF (84% [95% CI, 76%-90%]; 75% [70%-80%]). In regard of 5-year OS with an absence of GP data, TPF was associated with the highest rate (86%; 95% CI, 82%-90%), followed by PF (82%; 95% CI, 75%-88%) and TP (70%; 95% CI, 61%-79%). In addition, PF (90%; 95% CI, 86%-94%) had a higher ORR after induction chemotherapy compared to TPF (87%; 95% CI, 77%-94%), GP (79%; 95% CI, 33%-100%), and TP (78%; 95% CI, 39%-100%).

In comparison with two cycles of induction chemotherapy, three cycles of induction chemotherapy might slightly increase the 3-year LRFS (94% [95% CI, 92%-96%] vs. 89% [95% CI, 83%-94%]) and DMFS (91% [95% CI, 87%-95%] vs. 82% [95% CI, 76%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (93% [95% CI, 96%-87%]) rates, but fail to improve the ORR (95% CI, 96%-87%]) rates, but fail to improve the ORR (95% CI, 96%-87%]) rates, but fail to improve the ORR (95%-87%]) rates, but fail to improve the ORR (95%-87%)] rates, but fa

87%-97%] vs. 100% [95% CI, 100%-100%]) and DCR (92% [95% CI, 87%-95%] vs. 100% [95% CI, 99%-100%]) after the completion of CCRT.

Before the administration of platinum-based CCRT, patients who had received induction chemotherapy in the triweekly concurrent platinum therapy group had an 89% (95% CI, 85%-93%) of ORR and a 99% (95% CI, 99%-100%) of DCR that were much higher than the weekly group (65% [95% CI, 40%-86%]; 83% [95% CI, 74%-91%]). In addition, the triweekly group showed an increased 5-year FFS rate versus the weekly group (74% [95% CI, 71%-78%] vs. 68% [95% CI, 54%-80%]). However, patients in both groups achieved comparable rates of 3-year (87% [95% CI, 83%-92%] vs. 86% [95% CI, 80%-92%]) and 5-year (81% [95% CI, 76%-85%] vs. 80% [95% CI, 63%-92%]) OS.

Intensity-modulated radiotherapy (IMRT) has changed outcome of NPC patients significantly. Since threedimensional radiotherapy (3DRT) data failed to separate from published trials, pooled IMRT and two-dimensional radiotherapy (2DRT) results were sub-analyzed. The IMRT



group showed higher rates of post CCRT objective response at 3 months (99% [95% CI, 98%-100%] vs. 83% [95% CI, 74%-91%]), 5-year OS (84% [95% CI, 77%-90%] vs. 70% [95% CI, 64%-76%]), and 5-year PFS (77% [95% CI, 73%-80%] vs. 62% [95% CI, 55%-68%]). Additionally, IMRT could decrease the rate of distant metastasis compared with 2DRT (5-year DMFS: 87% [95% CI, 84%-89%] vs. 70% [95% CI, 63%-76%]).

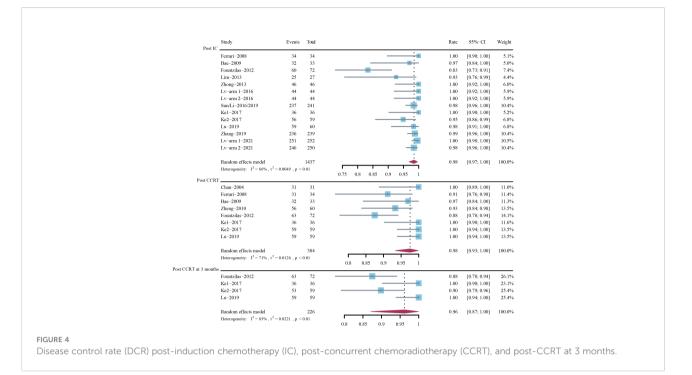
# Incidences of grade 3 or higher adverse events and subgroup analysis

For the meta-analysis, we focused on the hematological and non-hematological grade 3 or higher adverse events that were recorded during the induction chemotherapy and CCRT phases. A comprehensive list of the incidences of anemia, leucopenia, neutropenia, thrombocytopenia, febrile neutropenia, alopecia, diarrhea, fatigue, hepatotoxicity, mucositis, nausea/vomiting, and nephrotoxicity is provided in Figure 5B.

During the induction chemotherapy phase, the most common hematological grade 3 or higher adverse events were

neutropenia (27%; 95% CI, 18%-37%), leucopenia (17%; 95% CI, 9%-27%), and febrile neutropenia (8%; 95% CI, 4%-13%). The most common non-hematological grade 3 or higher adverse events were nausea/vomiting (7%; 95% CI, 3%-12%) and fatigue (6%; 95% CI, 2%-11%). Patients received TPF experienced the highest incidences of grade 3 or higher neutropenia (55%; 95% CI, 41%-69%), leucopenia (30%; 95% CI, 20%-40%), fatigue (12%; 95% CI, 8%-16%), and nausea/vomiting (17%; 95% CI, 12%-23%). Three cycles of induction chemotherapy induced more incidences of grade 3 or higher neutropenia (33% [95% CI, 21%-46%] vs. 22% [95% CI, 9%-39%]) and leucopenia (30% [95% CI, 17%-45%] vs. 6% [95% CI, 3%-11%]) against the two cycles group.

During the CCRT phase, the most common hematological grade 3 or higher adverse events were leucopenia (24%; 95% CI, 18%-31%), neutropenia (18%; 95% CI, 13%-24%), and thrombocytopenia (9%; 95% CI, 5%-14%). The most common non-hematological grade 3 or higher adverse events were mucositis (23%; 95% CI, 16%-31%), fatigue (12%; 95% CI, 9%-16%), and nausea/vomiting (12%; 95% CI, 4%-21%). Patients received TP induction chemotherapy had the highest



A			China	Non-China	TPF	PF	TP	GP	Two cycles	Three cycles	Weekly	Triweekly	2DRT	IMRT		
~	3-year O		0.88 (0.84-0.92)					4.94 (0.87-4.99)		0.88 (0.82-0.93)	0.86 (0.80-0.92)		0.77 (0.71-0.82)	0.91 (0.88-0.93)		
	3-year E		<u>0.79 (0.77-0.82)</u>		0.82 (0.78-0.85)	0.75 (0.70-0.80)	0.77 (0.71-0.83)	0.85 (0.92-0.90)		0.79 (0.75-0.82)	0.75 (0.71-0.90)	0.78 (0.74-0.82)	0.63 (0.47-0.78)	<u>0.30 (0.77-0.33)</u>		
	3-year D 3-year D		8.93 (0.92-0.95) 8.87 (0.84-0.91)		0.95 (0.91-0.98) 0.92 (0.87-0.97)		0.91 (0.87-0.94) 0.87 (0.83-0.90)	0.93 (0.90-0.96) 0.92 (0.88-0.95)		4.94 (8.92-4.95) 4.91 (8.87-4.95)	0.90 (0.81-0.96)	0.92 (0.90-0.94)	0.88 (0.83-0.92) 0.76 (0.69-0.81)	0.92 (0.89-0.94) 0.88 (0.86-0.90)		
								0.021008-0.051								
	S-year O		0.80 (0.75-0.84)				0.70 (0.61-0.75)		0.79 (0.71-0.85)		0.80 (0.63-0.92)		0.50 (0.64-0.56)	<u>9.84 (0.77-0.90)</u>		
	S-year F		0.73 (0.68-0.77) 0.87 (0.84-0.90)				0.80 (0.69-0.85)		0.72 (0.67-0.77)	0.74 (0.67-0.90) 0.87 (0.79-0.93)	0.68 (0.54-0.80)	0.28 (0.86-0.90)	0.62 (0.55-0.68)	9.77 (0.73-0.80) 9.90 (0.87-0.92)		
	S-year D S-year D		0.87 (0.84-0.90)				0.82 (0.71-0.91)		0.82 (0.25-0.97)		0.85 (0.74-0.93) 0.85 (0.65-0.98)		0.85 (0.79-0.89) 0.70 (0.63-0.76)	9.87 (0.84-0.87)		
	Post IC I	ORR RT ORR	8.87 (0.81-0.91) 8.99 (0.97-1.00)					0.79 (0.33-1.00) 0.92 (0.77-1.00)	0.84 (0.75-0.92)	0.85 (0.79-0.91) 0.93 (0.87-0.97)		0.98 (0.95-0.93)		4.90 (0.86-0.94) 4.99 (0.96-1.00)		
		DOIL CERT ORR	6.92 (6.97-1.00)			0.96 (0.92-0.99)		0.92 (0.17-1.00)		0.95 (0.90-0.97)		0.95 (0.95-1.00)	0.82 (0.18-1.00)	4.99 (0.94-1.90)		
	Pest IC I	DCR RT DCR	8.99 (0.99-1.00) 8.99 (0.97-1.00)		0.99 (0.97-1.00)		1.00 (0.98-1.00)	0.97 (0.88-1.00)	0.99 (0.98-1.00)		0.83 (0.74-0.91)	<u>4.99 (0.95-1.00)</u>	1.00 (0.95-1.00)			
	Parte	KIIAA	109 (009-100)	0.91 (0.85-0.96)	439 (034-130)	0.56 (#38-1.00)	1.00 (0.97+1.00)		1.44 (0.55-1.44)	432(03)-433)	0.32 (0.11-1.00)	0.98 (0.94-1.00)	0.37 (0.83-1.00)	0.99 (0.98-1.00)		
В		AE	Total	China	Non-China	TPE	PF	TP	GP	Two cycles	Three cycles	Weekly	Triserkly	2DRT	IMRT	
D	ō.	Accreia	0.01/0.00-0.03						0.01 (0.00-0.03)	0.00 (0.00-0.00)	0.02 (0.01-0.03				0.01 (0.00-0.02)	
	- interest	Leucapenia	0.17 (0.09-0.2			0.30 (0.20-0			0.11 (0.07-0.15)	0.05(0.03-0.11)	0.30 (0.17-0.45			0.01/0.00-0.045	0.15 (0.08-0.23)	
		Neutropenia	0.27 (0.18-0.3	) 0.27 (0.17-0.38)	0.28 (0.11-0.50	0.55 (0.41-0.4	0.13 (0.07-0.3	0.26 (0.06-0.52)	0.19 (0.15-0.25)	0.22 (0.09-0.39)	0.33 (0.21-0.46			0.21 (0.01-0.51)	0.25 (0.13-0.39)	
	- appe	Thranbocytopeni							0.05 (0.03 -0.09)	0.01 (0.00-0.04)	0.03 (0.00-0.09)		0.02 (0.00-0.04)		0.04 (0.01-0.07)	
		Febrile neutropeni	ia 0.08 (0.04-0.13	) 0.08 (0.03-0.13)	0.06 (0.00-0.17	0.09 (0.03-0.1	18) 0.03 (0.01-0.0	(6) 0.12 (0.03-0.25)		0.12 (0.03-0.25)	0.07 (0.03-0.12	0.12 (0.04-0.22)	0.04 (0.01-0.09)		0.45 (0.01-0.11)	
	ы к	Alopecia	0.01 (0.00-0.0	) 0.00 (0.00-0.01)	0.04 (0.00-0.25		0.04 (0.00-0.3	(4) 0.00 (0.00-0.02)	0.00 (0.00-0.24)	0.00 (0.00-0.01)	0.04 (0.00-0.25)	0.00 (0.00-0.02)	0.01(0.00-0.06)	0.26 (0.13-0.43)	0.00 (0.00-0.02)	
	^ §	Dianthea	0.02 (0.00-0.03	) 0.02 (0.00-0.03)	0.02 (0.00-0.05	0.04 (0.01-0.0	0.01 (0.00-0.0	(2) 0.00 (0.00-0.03)	0.01 (0.00-0.05)	0.00 (0.00-0.01)	0.03 (0.01-0.05)	0.02 (0.00-0.04)	0.01 (0.00-0.03)	0.05 (0.00-0.13)	0.02 (0.00-0.06)	
	20	Fetigne	0.06 (0.02-0.1		0.01 (0.00-0.09				0.00 (0.00-0.05)	0.05 (0.00-0.17)	0.06 (0.01-0.12)				0.48 (0.05-0.12)	
	ioj da	Beparetoxicity	0.03 (0.00-0.06						0.02 (0.00-0.04)	0.00 (0.00-0.01)	0.07 (0.00-0.19)	0.00 (0.00-0.01)		0.00 (0.00-0.02)	0.45 (0.00-0.16)	
	E.	Mucositis Nausca/Werniting	0.03 (0.01-0.04				(6) 0.02 (0.00-0.0 (3) 0.02 (0.00-0.1)		0.01 (0.00-0.03)	0.00 (0.00-0.01)			0.02 (0.01-0.03)		0.02 (0.01-0.04) 0.06 (0.02-0.10)	
	Nas	Nephrotonicity	0.00 /0.00-0.0		0.07 (0.0040.21		(1) 0.00 (0.00-0.0)		0.02 (0.01-0.04)		0.01 (0.00-0.07		0.01 (0.00-0.02)			
			0.06.03.04.0.0		0.02.49.00.0.04				0.08/0.05/0.120				0.66.03.03.0.10		0.10.00.00.10	
	100	Ascria	0.06 (0.04-0.0				(0) 0.06 (0.03-0.1 (3) 0.22 (0.15-0.1)		0.08 (0.05-0.12) 0.20 (0.15-0.25)	0.05 (0.03-0.11)	0.07 (0.03-0.11)		0.24 (0.16-0.33)	0.05 (0.01-0.11)	0.19 (0.11-0.27)	
	2	Neutropenia	0.18 (0.13-0.24						0.12 (0.08-0.16)	9.24 (0.13-0.36)	0.14 (0.08-0.20				0.21 (0.15-0.23)	
	loba	Thombocytopeni						(7) 0.10 (0.04-0.19)	0.07 (0.04-0.11)	0.09 (0.03-0.16)		0.10 (0.04-0.19)			0.13 (0.07-0.22)	
	Here	Febrile neutropeni		) 0.01 (0.00-0.02)	0.01 (0.00-0.04	0.00(0.00-0.0	(3) 0.01 (0.00-0.0	4) 0.04 (0.00-0.11)	0.00 (0.00-0.02)	0.04 (0.00-0.11)	0.01 (0.00-0.02	0.01 (0.00-0.02)	0.01 (0.00-0.03)	0.06 (0.00-0.18)	0.01 (0.00-0.04)	
	Ε.	Aktrocio	0.04/0.00-0.22	0.05 (8.09-0.33)	0.00/0.00-0.02		0.00(0)00-0.0	2. 0.18 (0.00-0.85)		1.02 (0.40-0.50)	0.00.00.00.0.02	0.00.00.00.000	8.46 (1.00.0.33)		0.00 (0.00-0.02)	
	5 6	Diambee	0.00 (0.00-0.0)	) 0.00 (0.00-0.01)	0.01 (0.00-0.07	0.00/0.00-0.0	0.00 (0.00-0.0	ND /	0.02 (0.00-0.04)	0.00 (0.00-0.00)	0.01 (0.00-0.02	0.00(0.00-0.01)	0.00 (0.00-0.02)		0.01 (0.00-0.02)	
	c bid	Fotigae	0.12 (0.09-0.14	0.14 (0.11-0.17)	0.09 (0.02-0.20	0.14 (0.11-0.1	9) 0.13 (0.06-0.1	9) 0.15 (0.04-0.29)		0.15 (0.04-0.29)	0.12 (0.08-0.16)	0.11 (0.05-0.18)	0.14 (0.10-0.18)		0.14 (0.10-0.18)	
	golo	Bepetetoxicity	0.02 (0.00-0.04		0.01 (0.00-0.03	0.45 (0.00-0.3		(9) 0.00 (0.00-0.02)	0.00 (0.00-0.01)	0.00 (0.00-0.01)	0.04 (0.00-0.14)	0.00 (0.00-0.01)			0.45 (0.00-0.16)	
	The second	Mucositis	0.23 (0.16-0.3)		0.36 (0.11-0.67				9.45 (0.13-0.79)	0.18 (0.10-0.29)	0.33 (0.26-0.42	0.30 (0.17-0.45)	0.20 (0.13-0.29)		0.15 (0.09-0.23)	
	j,	Nessea/Vomiting	g 0.12 (0.04-0.2) 0.01 (0.00-0.0		0.13 (0.08-0.19				0.07 (0.00-0.20)	0.10 (0.00-0.31)	0.13 (0.08-0.20) 0.04 (0.00-0.16)	0.23 (0.09-0.40)	0.05 (0.01-0.11)	0.04 (0.00-0.18)	0.21 (0.01-0.52)	
								(7) 0.00 (0.00-0.00)						0.00/00000011		

incidences of grade 3 or higher leucopenia (44%; 95% CI, 14%-77%), neutropenia (27%; 95% CI, 13%-44%), mucositis (20%; 95% CI, 4%-42%), and alopecia (18%; 95% CI, 0%-85%). More cases of grade 3 or higher neutropenia (24% [95% CI, 13%-36%] vs. 14% [95% CI, 8%-20%]) were reported in the two cycles group, while more cases of grade 3 or higher mucositis (33% [95% CI, 26%-42%] vs. 18% [95% CI, 10%-29%]) were reported in the three cycles group. Additionally, patients

treated with weekly platinum-based CCRT experienced higher incidences of grade 3 or higher mucositis (30% [95% CI, 17%-45%] vs. 20% [95% CI, 13%-29%]) and nausea/ vomiting (23% [95% CI, 9%-40%] vs. 5% [95% CI, 1%-11%]) compared to the patients in the triweekly group. In terms of radiation techniques, patients in the IMRT group showed higher incidences of grade 3 or higher leucopenia (15% [95% CI, 8%-23%] vs. 1% [95% CI, 0%-4%]) and nausea/vomiting

(21% [95% CI, 1%-52%] vs. 4% [95% CI, 0%-18%]) against the 2DRT group.

## Discussion

We performed a systematic review of induction chemotherapies and integrated the survival outcomes, responses, and toxic effects in patients with locoregionally advanced NPC who received induction chemotherapy and platinum-based CCRT. To our knowledge, this is the most comprehensive and largest meta-analysis of induction chemotherapy in NPC. Previous meta-analyses mainly demonstrated the benefits of adding induction chemotherapy to CCRT (9). Nevertheless, different populations, induction chemotherapeutic regimens and cycles, and even CCRT strategies may impact the efficacy and tolerability. A comprehensive analysis of the induction chemotherapeutic strategies reported in prospective clinical trials is essential, as the pooled data constitute a critical reference for clinicians. Significant heterogeneity existed among the enrolled studies, however, sensitivity analyses indicated that no substantial changes were found in the pooled survival outcomes and responses.

Although platinum-based induction chemotherapy significantly prolongs survival outcomes, whether adding 5fluorouracil to TP provides more benefits is hard to judge. Up to now, several studies have compared the efficacy and safety data between TPF and TP. Xiong et al. indicated that TPF failed to improve the OS and PFS in stage III-IV NPC patients compared with TP (53). A Bayesian network meta-analysis of prospective clinical trials involving 1570 patients found that TPF had the highest probability of being the optimal regimen versus TP and PF in terms of OS (50% vs. 47% vs. 2%) (54). In our analysis, we noticed that patients in both TP and TPF subgroups achieved nearly 100% of ORR after completing induction chemotherapy and CCRT. However, TPF had much higher 5-year OS (86% vs. 70%) and DMFS (90% vs. 82%) rates against TP. These results were consistent with the retrospective study published by Tao et al. that patients received TPF had better 5-year OS (85% vs. 79%; p = 0.037), PFS (85% vs. 77%; *p* = 0.008) and DMFS (90% vs. 82%; *p* = 0.004) rates than patients received TP (55).

The integrated 3-year survival rates of GP in our analysis showed satisfying effects in treating NPC patients, including 3year OS, FFS, and DMFS rates. In compared with TPF, GP showed a lower ORR after induction chemotherapy (79% vs. 87%) and comparable 3-year OS (94% vs. 92%), FFS (86% vs. 82%), LRFS (93% vs. 95%), and DMFS (92% vs. 92%) rates. In a comparative retrospective study, GP had a similar 3-year OS (94% vs. 92%), FFS (83% vs. 82%), LRFS (94% vs. 95%), and DMFS (90% vs. 90%) rates versus TPF, and no significant differences were observed (56). Nevertheless, GP induction chemotherapy was demonstrated to be cost-effective compared with TPF for locoregionally advanced NPC patients in realworld practice (57, 58). On the other hand, published data have demonstrated that TPF achieved significantly better 10-year OS than PF (HR, 0.58; p = 0.005), and the difference between TP and PF was marginally significant (HR, 0.71; p = 0.056) (59). Regarding the 5-year data, TPF regimen significantly improved OS (88% vs. 81; p = 0.042) rate compared with the PF regimen (60). However, according to our analysis, PF had a better 5-year OS rate than TP (82% vs. 70%) and showed the highest ORR after induction chemotherapy (90%), followed by TPF (87%), GP (79%), and TP (78%). It seems hard to deduce that PF is the lowest effective induction chemotherapeutic regimen.

Anthracycline-based induction chemotherapeutic regimens include epirubicin + paclitaxel + cisplatin, epirubicin + cisplatin, and epirubicin + mitomycin C + cisplatin + 5-fluorouracil. These strategies were mainly applied in the non-China population and Taiwan participants (21, 27, 41). In Fountzilas's study, locoregionally advanced NPC patients treated with epirubicin plus paclitaxel plus cisplatin had a 72% of ORR post-induction chemotherapy and an 83% of ORR post-CCRT (21). In Hong's report, the ORR after induction chemotherapy was 78% (41). In comparison with our pooled data, the addition of epirubicin to TP may not critically improve the responses in NPC patients. Moreover, since the unreversible cardiotoxicity, epirubicin has a 900 mg/m2 of maximum cumulative dose.

For CCRT strategies, triweekly platinum-based CCRT showed a higher 5-year FFS versus the weekly group (74% vs. 68%) in our analysis, but OS results were similar. A previously pooled analysis of retrospective studies showed no significant differences in 5-year survival outcomes between weekly and triweekly treatments (61). However, the weekly strategy may be associated with improved quality of life than the triweekly regimen (62).

The addition of induction chemotherapy to CCRT has revolutionized the treatment of locoregionally advanced NPC, but the efficacy deserves further elevated. Regardless of complete clinical remission is attained after induction chemotherapy and CCRT, patients may suffer a high risk of locoregional relapse or distant metastasis. Chen et al. reported a phase 3 clinical trial in 2021 and indicated that adding metronomic adjuvant capecitabine after CCRT significantly improved survival outcomes with a manageable safety profile (63). In the subgroup analysis of Chen's study, we noticed that only patients who received induction chemotherapy could benefit from adjuvant capecitabine treatment (FFS HR 0.49; 95% CI, 0.29-0.83) instead of patients who were treated with CCRT alone (FFS HR 0.51; 95% CI, 0.20-1.30). However, not all locoregionally advanced NPC patients are the suitable population for adjuvant chemotherapy. The changes of plasma EBV DNA across induction chemotherapy and CCRT may provide the necessity of the administration of adjuvant chemotherapy (64, 65). Finding out the suitable populations for induction chemotherapy plus CCRT, CCRT alone, and induction chemotherapy plus CCRT followed by adjuvant chemotherapy is meaningful for developing the treatment of NPC.

In terms of grade 3 or higher treatment-related adverse events, patients who received TPF regimen may suffer more incidences of

leucopenia (30%), neutropenia (55%), fatigue (12%), and nausea/ vomiting (17%) during the induction chemotherapy phase. In addition, three cycles of induction chemotherapy could induce more grade 3 or higher leucopenia (30%) and neutropenia (33%) versus two cycles. However, these toxicities are manageable. Thus, timely granulocyte colony-stimulating factor treatment could effectively prevent treatment-related severe adverse events or deaths.

## Strengths and limitations

The strengths of this analysis included (1) the results are supported by the large sample size from both single-arm and multi-arm prospective clinical trials, and (2) detailed subgroup analyses according to different populations, induction chemotherapeutic regimens, cycles, and CCRT strategies are displayed, because previously published meta-analyses mainly focused on the hazard ratios, odds ratios, or risk ratios in randomized studies comparing induction chemotherapy plus CCRT with CCRT alone or CCRT plus adjuvant chemotherapy. Nevertheless, our study has several limitations. First, heterogeneities existed among the enrolled studies. However, the large heterogeneity could mean that different clinical trials might exhibit inconsistent data of induction chemotherapy in treating locoregionally advanced NPC patients, which was the main point for us to conduct this meta-analysis to analyze the published data of induction chemotherapy comprehensively. In addition, a randomeffects model was adopted all through this study to address the heterogeneity. Second, patients were treated with different cycles of induction chemotherapy. The primary reason for the discontinuation of induction chemotherapy was the adverse events, but most of the enrolled patients received two to three treatment cycles. Fortunately, the two-cycle group was not inferior to the three-cycle group. Third, in the CCRT phase, concurrent chemotherapies comprised weekly and triweekly strategies. Although heterogeneities may increase accordingly, our subgroup analysis and previously published pooled analysis had indicated no significant differences between weekly and triweekly strategies.

## Conclusions

This meta-analysis has defined survival outcomes, response rates, and the incidences of treatment-related adverse events in locoregionally advanced NPC patients who received induction chemotherapy followed by CCRT. Different population and induction regimens may be associated with different survivals, responses, and adverse events. This global overview of the effects and risks of induction chemotherapies can provide a reference for clinicians and may guide clinical practice for patients with locoregionally advanced NPC.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

## Author contributions

B-CW and G-HL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, B-CW and G-HL. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript, B-CW, B-HK, and G-HL. Critical revision of the manuscript for important intellectual content, B-CW, X-XL, and QL. Statistical analysis, B-CW and G-HL. Administrative, technical, or material support, QL. Supervision, QL. All authors contributed to the article and approved the submitted version.

# Funding

This study was supported by the Hubei Provincial Natural Science Foundation (Grant number: 2020CFB397 to B-CW) and the Independent Innovation Foundation of Wuhan Union Hospital (Grant number: 2019-109 to B-CW).

# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fonc.2022.927510/full#supplementary-material

# References

1. Mao YP, Xie FY, Liu LZ, Sun Y, Li L, Tang LL, et al. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* (2009) 73:1326–34. doi: 10.1016/j.ijrobp.2008.07.062

2. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol (1998) 16:1310-7. doi: 10.1200/JCO.1998.16.4.1310

3. Chan AT, Leung SF, Ngan RK, Teo PM, Lau WH, Kwan WH, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* (2005) 97:536–9. doi: 10.1093/jnci/dji084

4. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol* (2016) 17:1509–20. doi: 10.1016/S1470-2045(16)30410-7

5. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med* (2019) 381:1124–35. doi: 10.1056/NEJMoa1905287

6. Tang LL, Chen YP, Chen CB, Chen MY, Chen NY, Chen XZ, et al. The Chinese society of clinical oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. *Cancer Commun (Lond)* (2021) 41:1195–227. doi: 10.1002/cac2.12218

7. National Comprehensive Cancer Network. Head and neck cancers (Version 3.2021). (2021).

8. Keam B, Machiels JP, Kim HR, Licitra L, Golusinski W, Gregoire V, et al. Pan-Asian adaptation of the EHNS-ESMO-ESTRO clinical practice guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck. *ESMO Open* (2021) 6:100309. doi: 10.1016/j.esmoop. 2021.100309

9. Wang BC, Xiao BY, Lin GH, Wang C, Liu Q. The efficacy and safety of induction chemotherapy combined with concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in nasopharyngeal carcinoma patients: a systematic review and meta-analysis. *BMC Cancer* (2020) 20:393. doi: 10.1186/ s12885-020-06912-3

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol (2009) 62:1006–12. doi: 10.1016/j.jclinepi.2009.06.005

11. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with r: a practical tutorial. *Evid Based Ment Health* (2019) 22:153-60. doi: 10.1136/ebmental-2019-300117

12. Ades AE, Lu G, Higgins JP. The interpretation of random-effects metaanalysis in decision models. *Med Decis Making* (2005) 25:646–54. doi: 10.1177/ 0272989X05282643

13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4

14. Chan ATC, Ma BBY, Lo D, Leung SF, Kwan WH, Hui EP, et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: Therapeutic monitoring with plasma Epstein-Barr virus DNA. *J Clin Oncol* (2004) 22:3053-60. doi: 10.1200/jco.2004.05.178

15. Ferrari D, Chiesa F, Codecà C, Calabrese L, Jereczek-Fossa BA, Alterio D, et al. Locoregionally advanced nasopharyngeal carcinoma: induction chemotherapy with cisplatin and 5-fluorouracil followed by radiotherapy and concurrent cisplatin: a phase II study. *Oncology* (2008) 74:158–66. doi: 10.1159/000151363

16. Bae WK, Hwang JE, Shim HJ, Cho SH, Lee JK, Lim SC, et al. Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer. *Cancer Chemother Pharmacol* (2009) 65:589–95. doi: 10.1007/s00280-009-1152-0

17. Huang PY, Mai HQ, Luo DH, Qiu F, Li NW, Xiang YQ, et al. Inductionconcurrent chemoradiotherapy versus induction chemotherapy and radiotherapy for locoregionally advanced nasopharyngeal carcinoma. *Chin J Cancer* (2009) 28 (10):1033–42. doi: 10.5732/cjc.009.10114

18. Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol* (2009) 27:242–9. doi: 10.1200/JCO.2008.18.1545

19. Kong L, Zhang YW, Hu CS, Guo Y. Neoadjuvant chemotherapy followed by concurrent chemoradiation for locally advanced nasopharyngeal carcinoma. *Chin J Cancer* (2010) 29:551–5. doi: 10.5732/cjc.009.10518

20. Zheng JJ, Wang G, Yang GY, Wang DY, Luo XZ, Chen C, et al. Induction chemotherapy with nedaplatin with 5-FU followed by intensity-modulated radiotherapy concurrent with chemotherapy for locoregionally advanced nasopharyngeal carcinoma. *Japanese J Clin Oncol* (2010) 40:425–31. doi: 10.1093/jjco/hyp183

21. Fountzilas G, Ciuleanu E, Bobos M, Kalogera-Fountzila A, Eleftheraki AG, Karayannopoulou G, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic cooperative oncology group (HeCOG) with biomarker evaluation. *Ann Oncol* (2012) 23:427–35. doi: 10.1093/annonc/mdr116

22. Huang PY, Cao KJ, Guo X, Mo HY, Guo L, Xiang YQ, et al. A randomized trial of induction chemotherapy plus concurrent chemoradiotherapy versus induction chemotherapy plus radiotherapy for locoregionally advanced nasopharyngeal carcinoma. *Oral Oncol* (2012) 48:1038–44. doi: 10.1016/j.oraloncology.2012.04.006

23. Huang PY, Zeng Q, Cao KJ, Guo X, Guo L, Mo HY, et al. Ten-year outcomes of a randomised trial for locoregionally advanced nasopharyngeal carcinoma: A single-institution experience from an endemic area. *Eur J Cancer* (2015) 51:1760–70. doi: 10.1016/j.ejca.2015.05.025

24. Kong L, Hu C, Niu X, Zhang Y, Guo Y, Tham IWK, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiation for locoregionally advanced nasopharyngeal carcinoma: interim results from 2 prospective phase 2 clinical trials. *Cancer* (2013) 119:4111–8. doi: 10.1002/cncr.28324

25. Lim AM, Corry J, Collins M, Peters L, Hicks RJ, D'Costa I, et al. A phase II study of induction carboplatin and gemcitabine followed by chemoradiotherapy for the treatment of locally advanced nasopharyngeal carcinoma. *Oral Oncol* (2013) 49:468–74. doi: 10.1016/j.oraloncology.2012.12.012

26. Zhong YH, Dai J, Wang XY, Xie CH, Chen G, Zeng L, et al. Phase II trial of neoadjuvant docetaxel and cisplatin followed by intensity-modulated radiotherapy with concurrent cisplatin in locally advanced nasopharyngeal carcinoma. *Cancer Chemother Pharmacol* (2013) 71:1577–83. doi: 10.1007/s00280-013-2157-2

27. Rosenblatt E, Abdel-Wahab M, El-Gantiry M, Elattar I, Bourque JM, Afiane M, et al. Brachytherapy boost in loco-regionally advanced nasopharyngeal carcinoma: a prospective randomized trial of the international atomic energy agency. *Radiat Oncol* (2014) 9:67. doi: 10.1186/1748-717x-9-67

28. Lee AWM, Ngan RKC, Tung SY, Cheng A, Kwong DLW, Lu TX, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* (2015) 121:1328–38. doi: 10.1002/cncr.29208

29. Lee AWM, Ngan RKC, Ng WT, Tung SY, Cheng AAC, Kwong DLW, et al. NPC-0501 trial on the value of changing chemoradiotherapy sequence, replacing 5-fluorouracil with capecitabine, and altering fractionation for patients with advanced nasopharyngeal carcinoma. *Cancer* (2020) 126:3674–88. doi: 10.1002/cncr.32972

30. Tan T, Lim WT, Fong KW, Cheah SL, Soong YL, Ang MK, et al. Concurrent chemo-radiation with or without induction gemcitabine, carboplatin, and paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* (2015) 91:952–60. doi: 10.1016/j.ijrobp.2015.01.002

31. Lv X, Xia WX, Ke LR, Yang J, Qiu WZ, Yu YH, et al. Comparison of the short-term efficacy between docetaxel plus carboplatin and 5-fluorouracil plus carboplatin in locoregionally advanced nasopharyngeal carcinoma. *Oncotar Ther* (2016) 9:5123–31. doi: 10.2147/OTT.S103729

32. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol* (2016) 17:1509–20. doi: 10.1016/S1470-2045(16)30410-7

33. Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, Sun Y, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of phase 3 randomized controlled trial. *Int J Cancer* (2019) 145:295–305. doi: 10.1002/ijc.32099

34. Tang CY, Wu F, Wang RS, Lu HM, Li GS, Liu ML, et al. Comparison between nedaplatin and cisplatin plus docetaxel combined with intensitymodulated radiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multicenter randomized phase II clinical trial. *Am J Cancer Res* (2016) 6:2064–75.

35. Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma:

A phase III multicentre randomised controlled trial. *Eur J Cancer* (2017) 75:14–23. doi: 10.1016/j.ejca.2016.12.039

36. Yang Q, Cao SM, Guo L, Hua YJ, Huang PY, Zhang XL, et al. Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial. *Eur J Cancer (Oxf Engl)* (2019) 119:87–96. doi: 10.1016/j.ejca.2019.07.007

37. Ke LR, Xia WX, Qiu WZ, Huang XJ, Yu YH, Liang H, et al. A phase II trial of induction NAB-paclitaxel and cisplatin followed by concurrent chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma. *Oral Oncol* (2017) 70:7–13. doi: 10.1016/j.oraloncology.2017.04.018

38. Ke LR, Xia WX, Qiu WZ, Huang XJ, Yang J, Yu YH, et al. Safety and efficacy of lobaplatin combined with 5-fluorouracil as first-line induction chemotherapy followed by lobaplatin-radiotherapy in locally advanced nasopharyngeal carcinoma: preliminary results of a prospective phase II trial. *BMC Cancer* (2017) 17:134. doi: 10.1186/s12885-017-3080-4

39. Kong L, Zhang YW, Hu CS, Guo Y, Lu JDJ. Effects of induction docetaxel, platinum, and fluorouracil chemotherapy in patients with stage III or IVA/B nasopharyngeal cancer treated with concurrent chemoradiation therapy: Final results of 2 parallel phase 2 clinical trials. *Cancer* (2017) 123:2258–67. doi: 10.1002/cncr.30566

40. Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). *Ann Oncol* (2018) 29:731–6. doi: 10.1093/annonc/mdx770

41. Hong RL, Hsiao CF, Ting LL, Ko JY, Wang CW, Chang JTC, et al. Final results of a randomized phase III trial of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with stage IVA and IVB nasopharyngeal carcinoma-Taiwan cooperative oncology group (TCOG) 1303 study. *Ann Oncol* (2018) 29:1972-9. doi: 10.1093/ annonc/mdv249

42. Wei JW, Feng HX, Xiao WW, Wang QX, Qiu B, Liu SL, et al. Cycle number of neoadjuvant chemotherapy might influence survival of patients with T1-4N2-3M0 nasopharyngeal carcinoma. *Chin J Cancer Res* (2018) 30:51. doi: 10.21147/j.issn.1000-9604.2018.01.06

43. Yang H, Chen X, Lin S, Rong J, Yang M, Wen Q, et al. Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a prospective, multi-center, randomized clinical trial. *Radiother Oncol* (2018) 126:37–42. doi: 10.1016/j.radonc.2017.07.020

44. Ghosh-Laskar S, Pilar A, Prabhash K, Joshi A, Agarwal JP, Gupta T, et al. Taxane-based induction chemotherapy plus concurrent chemoradiotherapy in nasopharyngeal carcinoma: Prospective results from a non-endemic cohort. *Clin Oncol* (2019) 31:850–7. doi: 10.1016/j.clon.2019.06.011

45. Jin T, Qin WF, Jiang F, Jin QF, Wei QC, Jia YS, et al. Cisplatin and fluorouracil induction chemotherapy with or without docetaxel in locoregionally advanced nasopharyngeal carcinoma. *Trans Oncol* (2019) 12:633–9. doi: 10.1016/j.tranon.2019.01.002

46. Lu Y, Chen D, Liang J, Gao J, Luo Z, Wang R, et al. Administration of nimotuzumab combined with cisplatin plus 5-fluorouracil as induction therapy improves treatment response and tolerance in patients with locally advanced nasopharyngeal carcinoma receiving concurrent radiochemotherapy: a multicenter randomized controlled study. *BMC Cancer* (2019) 19:1262. doi: 10.1186/s12885-019-6459-6

47. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *New Engl J Med* (2019) 381:1124–35. doi: 10.1056/NEJMoa1905287

48. Zhao C, Miao JJ, Hua YJ, Wang L, Han F, Lu LX, et al. Locoregional control and mild late toxicity after reducing target volumes and radiation doses in patients with locoregionally advanced nasopharyngeal carcinoma treated with induction chemotherapy (IC) followed by concurrent chemoradiotherapy: 10-year results of a phase 2 study. *Int J Radiat Oncol Biol Phys* (2019) 104:836–44. doi: 10.1016/j.ijrobp.2019.03.043

49. Al-Rajhi NM, Khalil EM, Ahmad S, Soudy H, AlGhazi M, Fatani DM, et al. Low-dose fractionated radiation with induction docetaxel and cisplatin followed by concurrent cisplatin and radiation therapy in locally advanced nasopharyngeal cancer: a randomized phase II–III trial. *Hematol/Oncol Stem Cell Ther* (2020) 14 (3):199–205. doi: 10.1016/j.hemonc.2020.05.005

50. Li YY, Tian Y, Jin F, Wu WL, Long JH, Ouyang JL, et al. A phase II multicenter randomized controlled trial to compare standard chemoradiation with or without

recombinant human endostatin injection (Endostar) therapy for the treatment of locally advanced nasopharyngeal carcinoma: Long-term outcomes update. *Curr Problems Cancer* (2020) 44(1):100492. doi: 10.1016/j.currproblcancer.2019.06.007

51. Lv X, Cao X, Xia WX, Liu KY, Qiang MY, Guo L, et al. Induction chemotherapy with lobaplatin and fluorouracil versus cisplatin and fluorouracil followed by chemoradiotherapy in patients with stage III–IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised, controlled, phase 3 trial. *Lancet Oncol* (2021) 22:716–26. doi: 10.1016/S1470-2045(21)00075-9

52. Yao ZX, Zhang B, Huang JL, Shi L, Cheng B. Radiation-induced acute injury of intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy in induction chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a prospective cohort study. *Sci Rep* (2021) 11(1):7693. doi: 10.1038/s41598-021-87170-6

53. Xiong Y, Shi L, Zhu L, Peng G. Comparison of TPF and TP induction chemotherapy for locally advanced nasopharyngeal carcinoma based on TNM stage and pretreatment systemic immune-inflammation index. *Front Oncol* (2021) 11:731543. doi: 10.3389/fonc.2021.731543

54. He Y, Guo T, Wang J, Sun Y, Guan H, Wu S, et al. Which induction chemotherapy regimen followed by cisplatin-based concurrent chemoradiotherapy is the best choice among PF, TP and TPF for locoregionally advanced nasopharyngeal carcinoma? *Ann Transl Med* (2019) 7:104. doi: 10.21037/atm.2019.02.15

55. Tao HY, Zhan ZJ, Qiu WZ, Liao K, Yuan YW, Zheng RH. Docetaxel and cisplatin induction chemotherapy with or without fluorouracil in locoregionally advanced nasopharyngeal carcinoma: A retrospective propensity score matching analysis. *Asia Pac J Clin Oncol* (2021) 18(2):e111–8. doi: 10.1111/ajco.13565

56. Zhu J, Duan B, Shi H, Li Y, Ai P, Tian J, et al. Comparison of GP and TPF induction chemotherapy for locally advanced nasopharyngeal carcinoma. *Oral Oncol* (2019) 97:37–43. doi: 10.1016/j.oraloncology.2019.08.001

57. Wu Q, Liao W, Huang J, Zhang P, Zhang N, Li Q. Cost-effectiveness analysis of gemcitabine plus cisplatin versus docetaxel, cisplatin and fluorouracil for induction chemotherapy of locoregionally advanced nasopharyngeal carcinoma. *Oral Oncol* (2020) 103:104588. doi: 10.1016/j.oraloncology.2020.104588

58. Yang J, Han J, He J, Duan B, Gou Q, Ai P, et al. Real-world cost-effectiveness analysis of gemcitabine and cisplatin compared to docetaxel and cisplatin plus fluorouracil induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma. *Front Oncol* (2020) 10:594756. doi: 10.3389/fonc.2020.594756

59. Peng H, Chen B, He S, Tian L, Huang Y. Efficacy and toxicity of three induction chemotherapy regimens in locoregionally advanced nasopharyngeal carcinoma: Outcomes of 10-year follow-up. *Front Oncol* (2021) 11:765378. doi: 10.3389/fonc.2021.765378

60. Liu GY, Lv X, Wu YS, Mao MJ, Ye YF, Yu YH, et al. Effect of induction chemotherapy with cisplatin, fluorouracil, with or without taxane on locoregionally advanced nasopharyngeal carcinoma: a retrospective, propensity score-matched analysis. *Cancer Commun (Lond)* (2018) 38:21. doi: 10.1186/s40880-018-0283-2

61. Tang J, Zou GR, Li XW, Su Z, Cao XL, Wang BC. Weekly versus triweekly cisplatin-based concurrent chemoradiotherapy for nasopharyngeal carcinoma: a systematic review and pooled analysis. *J Cancer* (2021) 12:6209–15. doi: 10.7150/jca.62188

62. Lee JY, Sun JM, Oh DR, Lim SH, Goo J, Lee SH, et al. Comparison of weekly versus triweekly cisplatin delivered concurrently with radiation therapy in patients with locally advanced nasopharyngeal cancer: A multicenter randomized phase II trial (KCSG-HN10-02). *Radiother Oncol* (2016) 118:244–50. doi: 10.1016/j.radonc.2015.11.030

63. Chen YP, Liu X, Zhou Q, Yang KY, Jin F, Zhu XD, et al. Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. *Lancet* (2021) 398:303–13. doi: 10.1016/S0140-6736(21)01123-5

64. Hui EP, Li WF, Ma BB, Lam WKJ, Chan KCA, Mo F, et al. Integrating postradiotherapy plasma Epstein-Barr virus DNA and TNM stage for risk stratification of nasopharyngeal carcinoma to adjuvant therapy. *Ann Oncol* (2020) 31:769–79. doi: 10.1016/j.annonc.2020.03.289

65. Hui EP, Ma BBY, Lam WKJ, Chan KCA, Mo F, Ai QH, et al. Dynamic changes of post-radiotherapy plasma Epstein-Barr virus DNA in a randomized trial of adjuvant chemotherapy versus observation in nasopharyngeal cancer. *Clin Cancer Res* (2021) 27:2827–36. doi: 10.1158/1078-0432.CCR-20-3519